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PREVENTIVE MEDICINE AT THE YALE UNIVERSITY SCHOOL OF MEDICINE, 1940-49*

JOHN R. PAUL

In 1940 the Yale University School of Medicine began an experiment in the field of medical education by creating a *Section of Preventive Medicine, as a division of its Department of Internal Medicine.*[1] No claim is made for priority with regard to this move, or that the idea was new, or that it should be repeated elsewhere. There was discussion at that time as to what the newly created division of the School should be called; what its functions should be; what place it should occupy among other departments of the School and how it could be integrated with other Medical School activities in general. Indeed the choice of the name—Section of Preventive Medicine —was not unanimous, for it was recognized that this term "preventive medicine" leaves much to be desired[2] and is actually no better than another somewhat boastful, but less familiar term, "curative medicine." Nevertheless, common usage of the term *preventive medicine* has increased, and this has led to its wide acceptance in this country. Apparently *any* effort today which aims at the prevention of disease is popularly called preventive medicine.

Actually such details of nomenclature and academic organization are not important—the basic decision is whether to regard preventive medicine as a medical specialty like *public health,* or a vague non-medical subject, like *human welfare* with applications in all branches of medical science,[3] or whether to assume that preventive medicine is actually part of clinical medicine and goes to make up what is today called *comprehensive medicine* or *holistic medicine.*[4] The last interpretation is the one now followed at Yale.

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* From the Section of Preventive Medicine.
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[1] The principles on which this new division of the School were founded have been described by Paul, J. R.: Yale J. Biol., 1940, *13,* 253.

[2] For definite comments on the term Preventive Medicine see Smith, G. and Evans, L. J.: Science, 1944, *100,* 39; and Galdston, I.: *Ibid.,* 1944, *100,* 76.

[3] *Synopsis of the practice of preventive medicine as applied in the basic medical sciences and clinical instruction at the Harvard Medical School.* Cambridge, Harvard University Press, 1929.

[4] See editorial, Holistic medicine, J. Am. M. Ass., 1948, *138,* 1158; and also Menninger, K.: Ann. Int. M., 1948, *28,* 318; and Evans, L. J.: Ass. Am. M. Coll., 1947, *22,* 25.

Interpretations of the term "preventive medicine." It may seem presumptuous for physicians or internists to adopt a parental attitude toward preventive medicine. To some it would seem that clinicians have at last, and somewhat naïvely, "discovered" public health. But clinicians are not so bigotted as to fail to recognize that preventive medicine, besides being part of clinical (or comprehensive) medicine, has numerous and growing ramifications which already touch a host of different human activities lying outside the sphere of its own immediate interests. These are: house construction, housekeeping, dietetics, environmental, industrial, personal and mental hygiene, to mention but a few. Preventive medicine has political, legal, social, and even religious aspects, and in some medical schools the attempt has even been made to bring the departments of preventive medicine under the wing of a university division of the social sciences. It becomes important, therefore, to keep our vision clear and to try to define the framework within which an academic department of preventive medicine might attempt to operate, with the realization that we are dealing with a philosophy rather than a technical craft.

But first of all some differentiation should be made between the concept of preventive medicine, as used here, and the whole field of hygiene and public health. Preventive medicine as used here is part of the doctor's job. Public health has been defined by Winslow,[5] and in reviewing his definition it is important to point out that the objectives are reached through the medium of organized community effort and the development of social machinery rather than through the medium of the medical profession. Today the public health field is rapidly expanding in various directions.[6] Some of these directions, such as those involving the public care of patients, fall directly within the physician's sphere of interest, *i.e.*, the two fields overlap here. But on the other hand some of the expansion has taken place

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[5] "Public health is the science and the art of preventing disease, prolonging life, and promoting physical [and mental] health and efficiency through organized community efforts for the sanitation of the environment, the control of community infections, the education of the individual in principles of personal hygiene, the organization of medical and nursing service for the early diagnosis and preventive treatment of disease, and the development of the social machinery which will ensure to every individual in the community a standard of living adequate for the maintenance of health." The words in brackets were added by Prof. C.-E. A. Winslow to his earlier definition which appeared in Science, 1920, *51*, 23.

[6] Another contemporary vision of such expansion has been recently summarized by Mr. Oscar R. Ewing, with the statement that: "Health is everybody's business and everybody must make it his business." The New York Times Magazine Section, September 19, 1948, p. 22. See also Derryberry, M.: Health is everybody's business. Pub. Health Rep., Wash., 1949, *64*, 1293.

along political, sociological, and other lines which the physician may be reluctant to follow. The questions are these: How far do physicians care to become identified with the administrative and political responsibilities essential for public health practices, with the organization of community effort, with the development of social machinery? And to what extent should physicians as a group identify themselves with the activities of the many ancillary groups which are so essential to the social welfare field? It is questionable whether the physician's talents lie in this direction. Perhaps a tendency on the part of the medical profession to stand aloof from these mundane things may reflect a "holier than thou," or a "wiser than thou" attitude; it is fairer to say that such an attitude is based on the fact that the respective philosophies of the physician and the health and the welfare officer differ. Such differences are not undesirable and imply no antagonism—quite the opposite in fact, for one field complements the other. It is a question of different interests. Physicians are apt to be interested primarily in disease—many of them are sentimental pathologists at heart. Disease is the positive thing for physicians and the absence of disease has a negative value. To the medical officer primarily interested in the welfare of his people health becomes the objective—its absence has negative values. Furthermore, physicians are more at home when dealing with *individuals* and their troubles, in contrast with the health officer who deals with groups. As a whole, clinicians are inclined to treat each individual somewhat differently, whereas the medical officer, representing municipal, state, or national government, is called upon to treat all individuals of the same age group alike. The individual or clinical approach calls for the exercise of *clinical judgment,* which is the physician's most unique asset and which, like other types of judgment, requires special "attention power" and cannot be spread about too thinly. It is different from the type of judgment useful in carrying out administrative responsibilities and in public education. On the other hand, there is no doubt that developments in certain areas of the public health field have proven and will prove to be of great educational and inspirational value to the medical profession; and it is also clear that individual doctors cannot carry out programs of disease prevention as efficiently as can health officers. These are but a few examples of the way the two fields complement one another.

Further attempts to define the physician's part in the academic picture of preventive medicine as it now exists will not be made here because the modern physician's functions are changing kaleidoscopically and because

the many divergent views would carry us far afield.[7, 8, 9] But one can inquire how the clinical concepts of preventive medicine can be best developed as an academic discipline in medical schools. It has seemed to us that one of the best academic approaches to this subject both in the classroom and the laboratory is primarily through the medium of *clinical epidemiology* or *clinical endemiology*. I do not wish to become enmeshed at this point in definitive discussions of: What is epidemiology?[10] But it should be emphasized that in certain centers in this country the concept of epidemiology is no longer limited to the study of epidemics or even to the study of infectious disease. Both epidemiology and endemiology, in the sense used here, are terms which today describe the *ecology of human disease, i.e.*, the circumstances under which any disease or injury occurs—whether that disease be an infection, a chemical poisoning, a surgical condition such as an accident—or whether the circumstances be endogenous or exogenous, and whether the group involved be familial, domiciliary, occupational, or what not. All the ills to which the human flesh is heir may be said to have their particular epidemiology, or their ecology, or, to use a term frequently employed in England, their *social pathology*. This primary approach may be as fundamental an introduction to preventive medicine as autopsy pathology is to clinical medicine. For if one is willing to study the circumstances under which a given disease occurs, one should be in a better position to prevent it—according to the clinical principle that treatment logically follows diagnosis.

This ecological approach to medicine is timely since during the past generation medical practice and clinical instruction in medical schools have come to be centered in hospitals. Modern medicine, having become more and more a hospital activity, demands that the apprentice work of third- and fourth-year medical students be almost entirely concerned with sick

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[7] Preface in *Preventive medicine in modern practice.* Ed. under auspices of Committee on Public Health Relations of New York Academy of Medicine by J. A. Miller, G. Baehr, and E. H. L. Corwin. New York, Paul B. Hoeber, Inc., 1942, pp. ix-x.

[8] See *Proceedings of the Conference of Preventive Medicine and Health Economics,* September 30 to October 4, 1946, School of Public Health, University of Michigan, Ypsilanti, University Litho-printers, 1947. See also Paul, J. R.: (note 1); Perkins, W. H.: J. Ass. Am. M. Coll., 1947, *22,* 160; Smillie, W. G.: *Ibid.*, p. 164; and Leavell, H. R.: *Ibid.*, p. 210.

[9] *Social medicine, its derivatives and objectives.* New York Academy of Medicine Institute on Social Medicine, 1947. Ed. by Iago Galdston. New York, The Commonwealth Fund, 1949.

[10] What and who is an epidemiologist? Am. J. Pub. Health, 1943, *32,* 414, 647, 759, 867, 1041, and 1279; also What is epidemiology? *Ibid., 38,* 852.

people in a hospital bed, or sick people in the dispensary. These sick people are isolated "specimens." They are segregated from their environment, removed from the circumstances under which they became ill, separated from their families, stripped even of their clothes; all of which is done to create a proper atmosphere for diagnostic study and careful management on the physician's part, free from outside distractions. It may be trite to point out that these outside "distractions" are the very things which the modern doctor, or the student interested in preventive medicine, needs to study also. For if one is to handle patients adequately, it is necessary to bring clinical judgment to bear not only on the patient, but also on the circumstances under which his illness arose. There is nothing particularly original about this. It is and has long been the heart and soul of family practice, but it has been gradually eliminated from hospital practice where analytical techniques for the examination of the patient or of specimens have come to dominate the field of internal medicine. A plea for this "return to the soil" attitude may sound like a plea for a "dead" period in American medicine, such as the one which occurred in Germany at the beginning of the eighteenth century—a period with a poverty of observation and a wealth of speculation. Possibly so, but I would regard it as a plea for a more comprehensive or integrative type of medicine in preference to the analytical approach so popular in the past decades. That American medicine needs something of this type has been expressed elsewhere.[11]

And yet one might well raise the question here as to whether the need for relating the patient to his native environment and all its attendant circumstances has not been the very thing which has brought Social Service Departments into being in most good hospitals, and, I presume, all teaching hospitals. Such departments have proven indispensable, but a point I wish to make is that the existence of a local Department of Social Service in a teaching hospital does not relieve academic clinicians of their responsibilities regarding "extra-hospital medicine." Physicians cannot put the whole responsibility of *social medicine* in the hands of lay social workers.

The development of academic and clinical concepts of preventive medicine has resulted in the establishment of a number of new Departments of Preventive Medicine, and/or Social Medicine and/or Hygiene in medical schools in this country. Abroad, particularly in England, there has been considerable ferment and perhaps more activity in the development of the

[11] Gregg, Alan: Ann. Int. M., 1949, *30*, 810.

clinical concepts of preventive medicine which they term "social medicine"[12] than may be the case here.

In Britain since 1943 three university Departments of Social Medicine have come into being: in Oxford, Birmingham, and Edinburgh. The case for social medicine as a subject worthy of university support has a great exponent in Professor John A. Ryle, Director of the Institute of Social Medicine at Oxford. In quoting Professor Ryle,[13] we should recall that his ideas on this subject are those of a clinician who believes that "the whole man and his family are still—or rather should be—the practising physician's charge, but they can no longer be considered in detachment from their total environment or from the larger communities of which they are but a part. Communities, large and small, are now due for a more intimate study and care in respect of their health and sickness, but they, too, cannot be considered in detachment from their total environment and from the individuals and families of which they are composed. The state is in the process of planning for larger measures of direction and organization and a wide extension of services, but state medicine—like clinical medicine—must in the end be based upon scientific principles and humane understanding. A good social medicine must in fact have its foundations in a sound social pathology."

And finally there is another function with which it would seem that university Departments of Preventive Medicine should be concerned, namely, that besides gathering and integrating data, some attention should be paid to the philosophy of the subject. It is possible that the age in which we live will be regarded by future generations as the age of "militant *preventive* medicine," in which man devoted his energies to attempts at stamping out disease in the same manner as some of our forefathers were concerned militantly with the stamping out of sin. If universities are not to be concerned with these policies it is hard to see what group will. It brings us to the fact that decisions of policy are easier for "curative physicians" than for "preventive physicians." The "curative physician's" policies were laid down long ago, perhaps by Hippocrates—medical schools

[12] The term "social medicine," as used in England, turns out to be quite close in its context to the clinical approach to preventive medicine outlined above. Social medicine is not popular in the United States, perhaps because it brings up visions of "socialized medicine." To us it also smacks more of legal, economic, or political concepts than of clinical concepts. This article carries with it no plea for the introduction of the term of *social medicine* in this country but merely that it be recognized in its true context. For further definitions, see Ref. 2.

[13] Ryle, J. A.: *Changing disciplines.* Lectures on the history, methods and motives of social pathology. London, Oxford University Press, 1948, pp. vi-vii.

have scarcely meddled with them since. But the extent to which a physician should interfere with a patient's life in attempting to cure him is more easily defined than the extent to which a physician should interfere with an apparently well person in trying to steer him away from future illness. Perhaps this can be settled by the patient or by the public and by what he or it is willing to pay for, and in this respect Mr. Ewing's statement quoted above is singularly apropos.[6] And yet if there are clinicians in the United States who have been concerned philosophically with the creation or moulding of the basic principles in this field, to my knowledge they have not been very vocal.[14] Actually the principles or hypothetical creed of preventive medicine does not seem to have been mapped by any special group. Our civilization has been literally swept along, bolstered up somewhat by Christian ideals and legal decisions as to what appears to be right. Most people have at least assumed it to be axiomatic for doctors (and everyone else for that matter) to prolong life at any cost and to prevent any preventable disease, as one would prevent trouble if possible. But further discussion of this cannot be carried on here. It would be a whole chapter in itself which would lead us into the biological aspects of disease, such as those to be found in the works of Charles Nicolle[15] and of Burnet.[16] The query here is whether physicians or biologists can rightfully assume that all human disease is necessarily bad and therefore that all disease should be prevented. Certainly the acquisition before puberty of mumps and German measles for boys and girls, respectively, is not "bad" at the present time. How bad different diseases are becomes a matter of mature judgment, perhaps mature clinical judgment. Clinicians or pathologists who are interested in the natural history of disease should be in a better position than most to map the basic ideas for disease control, and an opportunity is lost if medical schools do not recognize this fact.

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[14] In the United States there is no dearth of national organizations and their advisory committees which deal with preventive medicine and public health practices. These are identified with the American Public Health Association, the American Medical Association, and they also represent various governmental agencies, such as the U.S. Public Health Service, the Division of Medical Sciences of the National Research Council, etc. But to my knowledge these organizations and their consulting committees are mainly concerned with administrative policy, technical aspects, standards, and expediency with regard to preventive medicine. Their tasks remind one of the tasks which confront those committees often present in United States colleges and universities, appointed from faculty and alumni members, whose mandate is, to try to cope intelligently with the "problem of college football."

[15] Nicolle, Charles: *Destin des maladies infectieuses.* Paris, Felix Alcan, 1934.

[16] Burnet, F. M.: *Biological aspects of infectious disease.* New York, The Macmillan Company, 1939.

Review of activities at Yale. With this background we can turn now to the ten-year record of the Section of Preventive Medicine of the Yale University School of Medicine. It has been an experimental period which has included four war years. In this decennial report we should emphasize that our primary objective has been to champion the concept of preventive medicine outlined in earlier pages of this paper, and our primary effort has been to build along these lines the best Section of Preventive Medicine possible. In doing so we have not sought to expand activities which might overlap or infringe upon the work of other departments, but instead to strengthen our collaboration with those divisions of the School which are striving toward the same objectives and with which such collaboration is mutually advantageous. It is not a new technique which we bring, but a new philosophy. Our activities have naturally been concerned with teaching and with research work and practice, and in order to carry them out properly we have collaborated in many of the activities of the Department of Internal Medicine, the newly formed Division of Microbiology, and the Department of Public Health. To avoid duplication we have not attempted work in the fields of maternal and child hygiene, mental hygiene, cancer control, and many of the activities so well taken care of at present by various university and medical school departments.

Teaching. Formal courses have not been offered to students in their preclinical years.[17] Emphasis on the teaching of preventive medicine has thus fallen on students in their clinical years, *i.e.,* while serving in their third year as clerks on the wards of the Hospital and in their fourth year as assistants in the Dispensary. Simultaneously this teaching has also been directed towards internes, residents, and fellows who may be in various apprentice capacities in the Hospital and School of Medicine.

No attempt is made in our plan of teaching to train medical students to become health officers. We believe this training is of a specialized type and should be on the postgraduate level. Rather we have been guided in clinical teaching to train potential physicians and surgeons, to recognize and appreciate that preventive medicine will play an increasing part in the modern practice of medicine and surgery. To achieve this end the attempt is made to concern ourselves with those aspects of clinical medicine which may be said to lie *outside* of the immediate diagnostic and therapeutic consideration of hospital medicine. The point is made that hospital medicine,

[17] A single trial (given one year only) in the form of short series of elective lectures on "Introduction to Medicine and Public Health" was abandoned because of limited attendance on the part of the first-year students.

dealing as it does with sick people in bed, is but a small part of comprehensive medicine.

Secondarily, as already mentioned, we have tried to give our students some knowledge and familiarity with epidemiology, particularly clinical epidemiology,[18] in the belief that this is an appropriate foundation for instruction in preventive medicine. More time is spent in trying to inculcate "epidemiological thinking" than in teaching any special technique. At present there is no formal, required course in epidemiology *per se* listed in the curriculum of the Yale University School of Medicine, so there is no duplication here. The instruction in bacteriology received by students in the second year may be regarded as an introduction to epidemiology, but it actually is not epidemiology—nor has it been since Pettenkoffer's days. A major difficulty in suddenly attempting to impress third-year students with the importance of this subject is that it requires some biostatistical training and ability to think in terms of statistics. Our present curriculum does not include such training for medical students, and it is a deficiency which deserves to be rectified.

It has been apparent to us for some time that third- and fourth-year medical students are more interested in sick people than in preventive medicine as an abstract subject. Therapy is more impressive to them than prevention. Third-year medical students have arrived at the stage of their training in which they have begun to see patients and to participate in the work of the Dispensary and Hospital. The demands and responsibilities of being a clinician suddenly become the most absorbing matter with them, unless it be discussions on medical economics. For this reason we have found it advisable to organize a weekly seminar around one or more sick patients whom one or more of the students already know, and then to "lead the discussion gradually away from the bedside." We have found this approach to be more successful than that of assigning a given case, which may be an example of some special disease, to a third- or fourth-year student just for the purpose of having the case "worked up" from the social and environmental sides. In other words, we only utilize at present in the third-year course those patients to whom students have *already* been assigned as clinical clerks, whom they have come to know well, and in whose welfare they have become interested. The student is thus led to develop an interest in spheres of activity which lie outside the immediate care of his hospitalized patient. This interest concerns a much more complete review of the patient's past history than one usually finds in the

[18] Paul, J. R.: *J. Clin. Invest.*, 1938, *17*, 539.

average hospital record. It concerns an adequate family history with particular reference to the family environment, where and under what circumstances the patient has lived. And it concerns his occupational history. The value of conversations with members of the patient's family is stressed and the value of a study of the records of other members of the family who perhaps have previously been patients in the Grace-New Haven Community Hospital. When possible a visit by the student to the patient's home is advised; recently this has seldom been carried out—a situation which will be rectified. Finally the student is asked to consult with the Social Service Department whose members can review the situation with him from their angle. With this material at hand, students present these patients at a weekly preventive medicine seminar for third-year students serving as clinical clerks on the medical services. Most of the students may have already seen and examined the patients under discussion on ward rounds. This weekly conference group is comprised of about fifteen, including clinicians of both senior and junior grades, often a psychiatrist, occasionally public health physicians and an industrial physician, one or more social workers, and others who may be interested. After the case history has been presented it has been our aim to start the discussion with a critical review of the accuracy of the diagnosis, and a presentation of what is known about the epidemiology of the disease in question. If possible, some pertinent data are next shown, either on a lantern slide or in tabular form on the blackboard, to indicate certain known circumstances under which the disease in question usually occurs, together with a listing of various factors thought to be of etiologic importance or of importance as predisposing elements. The past history of the patient is then reviewed step by step in the light of the epidemiological data; the patient's present condition is reported and the prognosis discussed. All of these features are reviewed at some length *before* the attempt is made to predict how the situation which led up to the patient's illness might have been altered, how the situation should be handled from the standpoint of prevention *after* the patient leaves the hospital, and how a similar situation with another potential patient could be handled.

In the fourth-year teaching, the Section of Preventive Medicine has shared, for the past four years, with the Department of Public Health in conducting a required course designated as Preventive Medicine and Public Health, given largely in the form of lectures or demonstrations. The Section of Preventive Medicine is responsible for the first half of these lectures in which special subjects, including well-known diseases such as tuberculosis.

venereal disease, rheumatic fever, and poliomyelitis are reviewed from the control standpoint. This is the only formal, didactic teaching in which the Section engages. Occasionally authorities from outside the University faculty are asked to give some of these lectures. During the second half of the course and under the guidance of the Department of Public Health the fourth-year students are instructed in public health practices, in medical economics, medical jurisprudence, and hospital administration, and are given the opportunity to visit during field trips a tuberculosis sanitarium, a city health department, an industrial medical department, and one or two other institutions.

The elective courses given by the Section of Preventive Medicine are attended largely by fourth-year medical students, but not limited to that class. These include a course on the Principles of Epidemiology, one on Virus Diseases in Man, and one which provides an opportunity to do research work in the Section.

Research. By and large this has been in the field of clinical epidemiology and motivated by such questions as: To what extent can we hope to develop new ideas and new techniques applicable in the laboratory, in the hospital wards, in the dispensary, and, most of all, in field work, which will lead to a better understanding of the natural history of disease, or of disease as a biological phenomenon? A number of infectious diseases have received special investigative attention from this angle in this Section, including poliomyelitis, rheumatic fever, infectious hepatitis and serum hepatitis, infectious mononucleosis, and others. Work of this type might well be entitled Studies in Local (or Foreign) Social Pathology.

Practice. This has been largely represented by the activities of its clinical staff members in the hospital wards and dispensaries. These activities have included epidemiological consultations, and, as this is a new field for us, we have made no attempt to divorce the practical epidemiological work from that of clinical investigation in this field. Our department is not responsible for the carrying out of student or University employee health clinic programs but occasionally serves in a consulting capacity for such programs. Other "consulting" epidemiological activities have started at the local family level and extended to larger or more remote groups depending on circumstances. It has been our aim to work insofar as possible with the local, clinical material which comes to the Grace-New Haven Community Hospital. Nevertheless, such activities have not been limited to our local area but have been carried out in various regions of this country, Canada, and occasionally abroad, particularly for the United States Army. It is our

belief that the epidemiologist today who is called upon to develop the ecological concept of his subject should observe, if possible, the familiar diseases in which he is interested in various different environments. Facilities for doing this in our rapidly expanding world are fortunately greater than they were formerly.

Industrial medicine. In the original prospectus of work for the Section of Preventive Medicine,[1] industrial medicine was stressed as a major activity. During the period 1942-48 the Section was identified with the beginnings of work in industrial medicine on a full-time, or departmental basis within the School. For a period of four years we established and operated a local medical service for small plants.[19] Primarily this was done in an effort to see whether an intimate type of epidemiological data on sickness rates could be gathered in these small plants and subsequently broken down and analyzed in a fashion that perhaps might not be possible in larger plants. It depended on the plant doctor knowing the employees well. To a certain degree the objective was achieved, but it became apparent that the difficulties and responsibilities of running such a service were great, and that it eventually seemed wise to seek ways and means of acquiring the necessary data in other ways. A preliminary analysis of the original data required has, however, been published.[20]

In 1945 the Section participated in organizing a group of representative Connecticut industries to raise money and establish an Institute of Occupational Medicine and Hygiene at Yale University. This was done for various reasons, but in particular because the Connecticut State Medical Society through its Committee on Industrial Health had suggested that Yale University might concern itself with this important subject, a point of view with which the University was in accord. During its formative years the Institute was directed by a committee composed of representatives from the Department of Pharmacology, Section of Preventive Medicine, and the Department of Public Health; it now is entirely under the direction of the Department of Public Health.

We believe that the social pathology of an industrial community probably differs from that of an agricultural community and that the impact of industry on a community, as in southern New England cities and towns, is reflected in the local morbidity and mortality rates. In other words, epidemi-

[19] The New Haven Industrial Medical Service. Science, 1941, *95*, 187; Welt, L. G.: Yale J. Biol., 1942, *14*, 673; also The New Haven Industrial Medical Service. A summary of 3½ years' experience. J. Connecticut M. Soc., 1946, *10*, 193.

[20] Meigs, J. W.: Occup. Med., 1948, *5*, 11.

ological aspects of industrial medicine will continue to be a subject of interest to the Section of Preventive Medicine. Industrial medicine also continues to be a major field in which preventive medicine can be practised for the benefit of the adult civilian.

Conclusions

In summary, therefore, an outline of the interpretation of the subject Preventive Medicine has been presented, together with a Report of the Section of Preventive Medicine at the Yale University School of Medicine covering its first decade of life. To the reader it will be obvious that the interpretation is but one of many that could have been made, and that this division of the Medical School is still feeling its way and has much to learn.

OBSERVATIONS ON THE ROLE OF VAGAL ACTIVITY IN THE EFFECTS OF PULMONARY EMBOLISM*

JOSEPH H. CORT AND GEORGE D. DAVIS

Introduction

The clinical manifestations of sudden massive pulmonary embolism in animals usually include irregular tachypnea, feeble tachycardia and subsequent ecg changes, rapidly developing cyanosis, and fibrillation. Death ensues within a minute or so. Opinions as to the mechanism underlying these symptoms have differed. The hypothesis of a vagal reflex causing the shallow and rapid breathing of a post-embolitic subject was first advanced by Dunn,[3] and later Binger, Brow, and Branch[1] also showed that there might be a vagal element along with anoxia to explain the above respiratory phenomena. Steinitz, Megibow, and Katz,[4] on the other hand, working mainly on the cardiac changes of the post-embolitic subject, found no constant heart rate change, no striking systemic blood pressure change, and an occasional terminal ventricular fibrillation, and from this evidence conclude that pulmonary artery pressure changes resulting from blockage of the pulmonary circulation are alone adequate to account for the observed embolic symptoms and that termination of the subject is therefore by anoxia. The recent discovery by Walsh[5] that afferent impulses in the vagi are associated with experimental pulmonary embolism caused by starch granules reopens the controversy of neural versus pressure factors in pulmonary embolism.

This work was undertaken to investigate further the possibility of neural participation in the symptomatology. It consists of simultaneous recording of systemic blood pressure, frequency and amplitude of respiration, and the electrocardiogram in the terminal events in embolized animals with the vagi intact, with the vagi severed, and with a previous injection of atropine in animals with intact vagi. Finally direct clamping of the pulmonary artery was attempted in the dog, with no previous variables injected into the experiment, while the same measurements were made.

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Methods

Cats were the principal animals used in this series of experiments and all were worked on under Dial anesthesia. Systemic blood pressure was recorded from the carotid by means of a siliconed heparinized needle leading to a Statham pressure transducer ("strain gauge") coupled with a beat frequency oscillator.* This in turn was fed into a Grass push-pull amplifier and recorded by means of a mechanical pen-writer. Respiration was recorded by means of an impedance plethysmograph[3] where the varying resistance was the distance across the chest cavity at the lateral angles of rib 10 on both sides. This was also fed into a Grass amplifier and pen-writer, as were the standard electrocardiograph leads. All recording was done simultaneously. Lead I was the most frequently used in the electrocardiograph recording. Starch granule emboli were administered to the animals by very rapid injection of 4 cc. of a suspension of starch granules in physiological saline (1 g. pure unhydrolyzed starch granules per 5 cc. saline) into the saphenous vein. The average injection time was but a few seconds, done so as to provide the pulmonary circulation with a sudden burst of blocking particles which would more nearly simulate the sudden complete blockage of a fatal clinical embolus than would a slower injection time. On such animals the lungs were removed postmortem and sections were made with both iodine and H&E as the staining agent. Samples of the carotid blood were also examined postmortem for presence of starch granules (by means of the color reaction with iodine) in order to determine whether any starch got through the lungs. When a direct approach to the pulmonary artery was desired, this was made through the anterior chest wall. Three cats were used with intact vagi, three with severed vagi, and two were atropinized. Two dogs were used in the clamping experiment.

Results and discussion

I. Animals with vagi intact. These animals began to show typical embolic symptoms even before the rapid injection was completed. All animals showed the same sequence of events. The 4 cc. of starch suspension were injected at a constant rate during a ten-second period. Eight seconds after commencing the injection the systemic blood pressure began to fall from the pre-injection mean of 200mm. Hg. Six seconds following the completion of the injection the mean pressure had plummeted to 20mm. Hg and all signs of pulsatile pressure had disappeared. Ten minutes later the mean pressure was zero.

Within eight seconds after completion of the injection, respiration, which had maintained an average rate of twenty-four movements per minute before the time of the injection, had increased to sixty to seventy movements per minute, and had become very irregular in both frequency and amplitude. At times the respiratory record showed Cheyne-Stokes

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* We wish to thank Dr. Samuel Gelfan for demonstrating his own arrangement of this coupling.

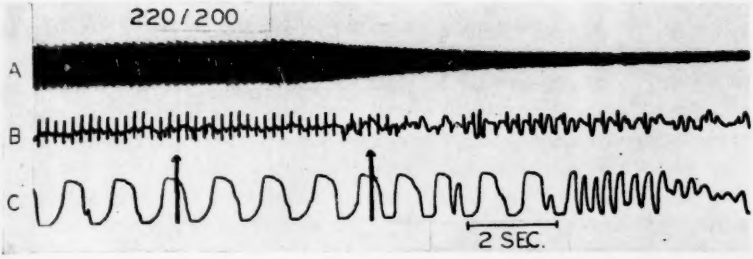

FIG. 1. Simultaneous record of blood pressure (A), ecg lead I (B), and respiration (C) (inspiration is an uptrace) in an embolized animal with vagi intact. The arrows denote the beginning and end of the starch injection. The measured time interval refers to all three records. The figures above line A indicate systolic pressure over diastolic pressure calibrated at that specific point in the record.

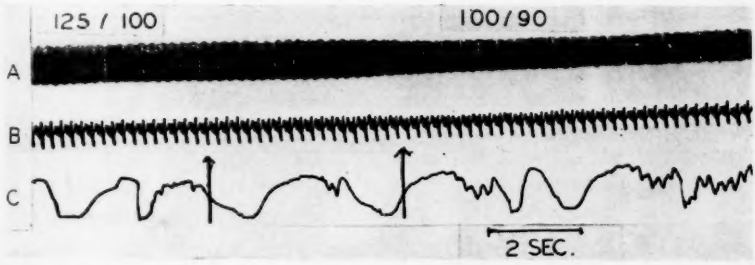

Fig. 2. Similar recording in an animal with severed vagi upon the administration of an embolus. The blood pressure record consists of the tracing from our oscillator (working at about 50 cycles per second), with the amplitude of each oscillation being a measure of the pressure at that instant. This amplitude is recorded on both the top and bottom sides of the mean line; thus when there is a pressure change both the tops and bottoms of the oscillatory tracings diverge or converge. In this manner we have subdivided our record into individual measurements of pressure every 1/50th of a second, thus easily picking up the systolic and diastolic differences when they exist.

characteristics. Ten minutes after completion of the blockage the thoracic muscles had begun to fasciculate, presumably from anoxia.

The electrocardiogram showed its initial changes just prior to the termination of the injection, consisting in varying marked changes in voltage, and perhaps a skipped beat. About five seconds following completion of the injection the typical electrocardiogram of pulmonary embolism developed. This consisted of an S-T depression with staircase ascent, and the appearance of a pronounced S wave. In a few minutes the beat had become very sluggish and showed complete dissociation of auricular from ventricular beat. Further developments, all within ten minutes, showed inversion of the T wave and progressive voltage decline. At this point it is difficult to say which of these changes were due to nervous influences and which were due to pressure phenomena.

A postmortem histological examination of the lungs showed little more than a slight congestion and a plugging of all observable arterioles with starch granules. An examination of the postmortem carotid contents failed to reveal any trace of starch granules. We may therefore conclude that the pulmonary circulation was the end-point in the vascular distribution of the starch. The simultaneous records of respiration, systemic blood pressure, and electrocardiogram, during and directly after the injection, are shown in Fig. 1.

II. Animals with severed vagi. The records obtained from these animals were strikingly different from those obtained in the previous series of experiments. Most interesting was the observation that more than twelve minutes had elapsed following injection before the systemic blood pressure reached a level of 20mm. Hg. In the animals with intact vagi this level had been reached in eight seconds. Moreover, the pressure drop in the first series had been quite precipitous, while in the vagotomized animals the fall was slow and linear throughout its course.

Respiration remained at substantially the same frequency until immediately prior to the death of the animal although the thoracic muscles lost the smooth contraction of the normal state and in the records (Fig. 2) appear to have a ragged and disconcerted action. The electrocardiogram was normal for about two minutes following the injection, subsequent to which an S-T depression began to develop. In another three minutes the S-T depression was quite marked. Aside from a slight voltage decline there were no other changes. This is in marked contrast to the findings in the animals with intact vagi. The histological findings in the postmortem lungs in this case were exactly the same as in the previous animals, and the

carotid contents showed no starch granules. The same picture was presented by all the vagotomized animals.

III. Animals with intact vagi, but with an injection of 2 mg. atropine per kilo one minute before the starch injection. In general these animals showed intermediate results between the two extremes already reported. The mean systemic blood pressure required 40 seconds to descend to a mean value of 20mm. Hg from an initial value of 200mm. Hg. Pulsations were still slightly evident at this point. Two minutes following injection respiration had become irregular and faintly cyclical in frequency, but at no time did it become nearly as rapid as the respiration in the animals with intact vagi. In the electrocardiogram, the S-T depression appeared within a few seconds and there was also a slight voltage decline, although the rate remained quite constant throughout. No other abnormalities appeared until ten minutes had elapsed, at which time signs of A-V dissociation were noted. As in the other two experiments, the postmortem lungs showed negligible change and the starch was shown never to have been carried beyond the lungs.

IV. Experiments on the effect of clamping the pulmonary artery. Dogs were used here since they offer larger anatomical structures and therefore provide a better surgical risk. The same recording techniques as before were used in this series. In each experiment clamps were suddenly applied to one of three positions on both of the pulmonary arteries. The locations used were: (i) just as the arteries emerged from the mediastinum; (ii) in the center of their free course; and (iii) just at the point of entry into the hilus of the lung. The rationale of this approach was to attempt to localize the position of the pressure receptors which are thought to be responsible for the nervous effects of pulmonary embolism. Except for a slight fall in systemic blood pressure, no change whatever was noted when the clamps were applied for periods as short as a few seconds. When the clamps were applied for a matter of minutes, an S-T depression was noted, as well as the above-mentioned pressure decline. We could achieve, therefore, some pressure manifestations, but no nervous component at all.

Conclusions

From the preceding evidence it seems fair to assume that vagal activity plays a very definite role in the symptomatology of multiple pulmonary embolism. This vagal activity would be primarily efferent. Whether afferent impulses travel through the vagus or by an entirely different pathway is a question yet open to experimental study. Our attempt to discover

receptors in the walls of the pulmonary arteries was unsuccessful, and we must conclude that if the changes resulting from pulmonary embolism are brought about by the action of increased pulmonary blood pressure on nervous receptors, these organs lie distal to the hilus of the lung.

The effect of the vagally transmitted impulses may be shown by the contrast of the effects of artificial embolism in normal and vagotomized animals. The difference in the rate of decline of systemic blood pressure suggests that vagal afferents affect the vasomotor center adversely in this situation thus leading to a rapid decline in both pulsatile and mean systemic blood pressure. As pointed out in previous work,[1, 3] there seems to be a definite vagal influence on the production of tachypnea by multiple pulmonary embolism. Finally, the electrocardiogram changes seem to be a result of both direct pressure and vagal effects. Since the S-T depression is a constant finding, with or without an intact vagus, it seems a safe assumption that it is due to the sudden load upon the right side of the heart and the resulting axis deviation. However, such changes as pronounced voltage decline, marked rate change, extrasystoles (both auricular and ventricular), dissociation, spread of the ventrivular complex, inversion of the T wave, and the development of an S wave, all seem to be initiated by nervous activity.

In attempting to produce a functionally vagotomized animal by atropine injection, intermediate results were obtained. With a view toward atropine protection against these effects of pulmonary embolism, the experiments certainly indicate a possibility of effective action which might be improved by a better dosage level.

No lung histopathology developed, which is thought to be due to the very short period between the experimental embolus and the death of the animal.

As to possible clinical significance, there are several points to be argued. Since the total effect could not be produced by direct clamping of the artery in its free course, the main question is the relation between the clinical etiology of a large clot embolus and the experimental etiology of a suspension embolus, where the difference in size would mean a difference in point of circulation blockage. The only way to equate these as to physiological effect is to note the time for the gamut of post-embolitic symptoms to occur. Since the same immediacy and extremely short duration holds for both the suspensoid and mass embolus, it can be argued that both cause a physiologically equivalent pressure rise. It must be also established that analogies would only apply to clinical cases of very rapid

embolitic death, since slow clinical embolitic terminations are probably mostly due to anoxic and pressure changes.

Summary

It has been found that the vagus plays a definite role in the following symptoms of multiple pulmonary embolism: rapid decline in systemic blood pressure, dissociation of auricular from ventricular beat, extrasystoles, voltage decline in the ecg, slowed cardiac rate, spread of the ventricular ecg complex, development of the S wave in the ecg, and inversion of the T wave.

The authors agree with previous investigators[1,3] who claim that vagal activity produces tachypnea in embolic subjects.

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WITCH'S MILK AND WITCHES' MARKS*

THOMAS R. FORBES

The term *witch's milk,* referring usually to the mammary secretion of newborn infants,† is an example of that small group of medical and biological words and phrases which had its origin in the popular vocabulary of past centuries. (*Freemartin*[22] is a similar term.) Such expressions lack the classical dignity of Greek and Latin ancestry, but they have a flavor and interest of their own. What was the source of the phrase *witch's milk,* with its implications of superstition and sorcery, and how has it persisted to take its place in modern scientific terminology?

Although little attention is given to the phenomenon in modern textbooks of pediatrics, it is well established that during the first weeks after birth the mammary glands of some babies hypertrophy and produce a colostrum-like secretion. Normally the secretion soon ends, and the glands regress. Partly on the basis of an important study by Lyons,[26] it is now generally believed that two maternal hormones, estrogen and prolactin, which during the later stages of pregnancy are preparing the maternal mammary glands for lactation, may escape into the fetal circulation in sufficient quantity so that the same phenomenon appears in the infant. If this theory is correct, the transitory production of witch's milk can be explained by the obvious fact that the availability to the baby of the maternal hormones ceases at birth. However, since prolactin has also been found in the pituitary glands of fetal calves,[6] it is possible that a brief activity of the baby's pituitary gland may also help to account for the appearance of the secretion.

To turn from the significance of the phenomenon to the significance of the phrase is to look back on the dark and evil history of witchcraft, on a record of inspired ignorance, unresisting credulity, and complacent cruelty. The record is certainly incomplete, and part of it is very nearly inaccessible. For our purposes a start may be made with an ancient belief that there existed a variety of demons which had the appearance of birds.[32] These creatures, feared because they were thought to suck the blood of infants, were called *Striges.* (The scientific name *Strigidae* much later was applied

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* From the Department of Anatomy and the Historical Library. Presented before the Beaumont Club on December 16, 1949.

† According to Marshall,[27] witch's milk may also appear in the newborn young of other mammals; the present paper will be concerned only with the human manifestation.

to the owl family, and the vampire tradition has not yet died.) Thomas Erastus (1524-1583), the Swiss theologian, says that Ovid mentioned the *Striges*. Erastus adds another belief: ". . . les anciens croyoyent [*Striges*] venir la nuict trouver les enfans & leur succer les mamelles."[21] Pliny the Elder discounts the *Striges* legend; he says the creatures were bats.[35]

In the seventeenth century, Johann Bohn described newborn infants (translated) "whose breasts swell with serous milk; if this is not expressed promptly and properly, they [the breasts] will become indurated and inflamed and will suppurate."[12] Although Bohn's case was one of the earliest which the author has been able to examine in the original, many previous instances of infant lactation must have been observed. At any rate, here were the elements of the situation—on the one hand, a recognition of the phenomenon as recorded; on the other, a sample of the related superstitions.

Not only were *Striges* and other evil spirits believed to victimize babies, but it was thought that witches—women accused of having sold their souls to Satan in return for the gift of supernatural powers—could suckle their imps or "familiars" from the mammary glands or from "teats" on other parts of the body.[14] Podmore has stated[43] that the superstitions regarding both the imps and the witches' teats occurred chiefly in Great Britain and the United States, but this opinion is not supported by evidence to be presented later. The "teat" constituted one of the several varieties of "witches' marks," and women accused of witchcraft were sometimes searched for such indication of their traffic with the forces of evil. A contemporary account of an "examen of witches" in France at the beginning of the seventeenth century, mentioning the inspection of the body of an accused woman for such supposed evidence, states that ". . . all witches have a mark some on the shoulder, some on the eyelid, some on the tongue or lip . . ."[11] In England there was repeated reference at witchcraft trials to the suckling of imps by witches and to attacks by imps on children for the same purpose. The imps were usually said to appear in animal form.[1, 2, 3, 38] It is shocking to realize that accusations of this sort and the findings of "teats" (very likely warts or similar structures or, in rare cases, supernumerary nipples) constituted evidence of guilt, but the accounts of the witchcraft trials are convincing. An unpopular individual, often elderly and eccentric, would be accused in vivid detail, torture would usually extract a "confession," and execution at gibbet or stake would follow swiftly. It has been estimated that 30,000 persons were put to death for witchcraft in England alone.[5]

New England had its share of witchcraft trials (see, for example, Calef,[18] Hutchinson,[21] and Mather[33]), and the witch's milk superstition appeared here too. It is encouraging to discover that in this country, as in Europe, courageous men raised protests against the hysteria. Robert Calef, a Boston merchant who died in 1720, struck out vigorously. He comments on the case of Mary Easty, hanged as a witch at Salem in 1692: "It seems, besides the testimony of the accused and confessors, another proof, as it was counted, appeared against her: it having been usual to search the accused for teats, upon some parts of her body . . . was found an excrescence which they called a teat."[18]

Francis Hutchinson, D.D., criticizing bitterly the witchcraft trials, discusses "teats" and other witch marks:

> *Jur.* What Judgment must we make of what they say about *Teats* and *Magical Signs,* as they call them; and insensible Parts that are found upon them?
>
> *Clerg.* I make no doubt but that some of them are *Scurvy-Spots,* or mortified or withered parts, or hollow Spaces between the Muscles: Others are *Piles* or *Verrucae Pensiles,* hanging Warts, which in Old Age may grow large and fistulous.[21]

Elsewhere Hutchinson states:

> I meet with little Mention of *Imps* in any Country but ours, where the law makes the feeding, suckling, or rewarding of them to be a Felony; but amongst our Witch-finders, it hath been a Rule,
>
> That the suspected Witches may be watched till their *Imps* appear; and their Imps may come in the Shapes of *Cats, Dogs, Rats, Mice, Spiders, Fleas, Nits, Birds, Flies, a Toad, a Frog, a Hen, a Crow, a Hornet, or a Mole.*[21]

Cotton Mather, thundering against the powers of darkness and encouraging the seeking out of witches, relates in 1693: "Among the Ghastly Instances of the *Success* which those Bloody Witches have had, we have seen even some of their own Children so dedicated unto the Devil, that in their Infancy it is found that the *Imps* have sucked them, and rendred them venomous to a Prodegy."[33]

Meanwhile, additional cases of infant lactation were appearing in the medical literature; curiously enough, the authors make no mention of witchcraft. Anton Deusing mentions that the mammary glands of infants of both sexes contain a milky secretion,[19] and Théophile Bonet records the phenomenon in a baby girl.[13] Diemerbroeck has a similar observation.[20] In addition, discussing the nutrition of the fetus, he states that since newborn babies may vomit a milky fluid before they have been fed, they probably draw milk from their own mammary glands *in utero.* He cites as an example the case of his own baby daughter. As Guillot[25] and Brouha[15] point out, Boerhaave supported this idea, calling attention to the posture of the fetus

in the uterus— ". . . it lies there in a bending Posture with its Head inclined forward."[9,10] Morgagni also referred to infant lactation.[30]

Medical notes on witch's milk appeared much more frequently during the nineteenth century. Textbooks began to include mention of the phenomenon.[8,18,34] In the journals, Goldschmidt,[25] Battersby,[7] Guillot,[28] and Gubler,[27] to mention only some of the authors, all described cases. There was disagreement as to whether the secretion actually was milk, but the point was settled, at least for the time being, by chemical analysis. In 1859 one case of witch's milk in a boy aged four weeks was described in the *Lancet,*[5] and during the summer of 1874 no less than fifteen communications on the subject were printed or summarized in the *British Medical Journal.*[4] Repeated reference was made to the midwife's or nurse's insistence on the necessity for the removal of the secretion, a procedure earlier described by Bohn,[12] Morgagni,[30] and Boerhaave. The latter remarks, ". . . the Nurses usually empty them [the mammary glands] . . . to prevent the stagnating Liquor from causing Disorders."[10] The injury likely to result from such a practice and from attempts to "break the nipple strings" was emphasized in the *British Medical Journal* contributions.[4] Knott, in an interesting discussion of witch's milk, states that when he was a medical student it was still customary to express the secretion from afflicted babies.[33] As will be shown later, this harmful procedure, condemned to the present day,[40] probably had its origin in lingering superstitions regarding witch's milk.

Among the numerous additional medical descriptions of the phenomenon which have appeared in the literature there is virtually no comment on the term. Actually, the phrase itself does not appear, among the large number of documents examined by the author, until the latter part of the nineteenth century. Since the superstition seems to have been an ancient one, *witch's milk* presumably had been in use for centuries, but proof of this supposition, in spite of an extensive search, has not been found. A major link in the history of the term is thus still missing.

Knott mentions that witch's milk was said to have been an ingredient of witches' brews.[33] Certainly there were many other superstitions regarding milk (see, for example, Kittredge[32] and Wuttke[41]). Thus, witches were believed able to obtain milk from the leg of a milking stool. As a result of evil influences, cows went dry or produced red or blue milk, and cream would not turn to butter. Numerous other strange superstitions related to childbirth, and midwives were sometimes thought to possess supernatural powers.

The French equivalent of *witch's milk, lait de sorcière,* appears in Frey's

histology textbook of 1871,[28] and has been referred to recently by Courrier.[37] The German word is *Hexenmilch.* As with the English expression, one cannot be sure how early the French and German terms became part of the respective languages. *Hexenmilch* was employed in a technical article by Genser in 1876,[24] but must have already been an established expression, since it is discussed in the famous Grimms' *Wörterbuch* of 1877.[26] Variants on the term were *Drachenmilch, Zaubermilch, Teufelsmilch, Hundsmilch,* and *lac magicum, incantamentis acquisitum* (*i.e.,* magical milk, obtained by incantations). Most unfortunately, there is no comment on the Latin phrase. Apparently the German words could refer to witch's milk in the modern sense, to the milk of a witch, to milk drawn from an axe handle by a witch, or even to the sap of the plant *Euphorbia,*[38] a member of a family of trees, shrubs, etc. distinguished for their unpleasant and sometimes milky and toxic juices. Here, surely, is a problem for the etymologist.

More recent German sources add further details. Ploss states that in Germany, and also in England and Naples, midwives and grandmothers were convinced that if witch's milk were not frequently and thoroughly expressed from the baby's mammary glands, it would be stolen by witches and goblins.[42] According to Höfler, *Hexenmilch* referred to enchanted, colored milk from a cow, to the product of infant lactation, and to the juice of the plant *Chelidonium majus*[39] (a member of the poppy family, and once used to cure warts—regarding which there are also superstitions). Höfler mentions the belief that evil spirits, goblins, or imps cast the evil eye on babies in order to induce the formation of *Hexenmilch* and thus provide themselves with a source of nourishment (cf. Hutchinson,[31] above). This superstition is confirmed by Hovorka and Kronfeld, who add that in Switzerland the appearance of lactation in a baby would evoke the statement (translated): " 'He has an imp' [Es hat das Schratteli]. This milk must be sucked out, and a knife with the edge uppermost is laid in the cradle."[30] Presumably the knife was expected to repel the imp. Peter describes a Westphalian remedy, which was to make an ugly puppet, resembling the bewitched infant, from rags and straw and then either to place the puppet in the baby's cradle or to nail the *Caricatur* over the door of the room.[41]

The witch's milk story seems to be, basically, the record of successive attempts to account for a readily observed biological phenomenon. Man is uncomfortable without a satisfactory explanation for a mystery. Such an instinct has engendered much superstition, and much science.

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THE METABOLIC RESPONSE OF INFANTS TO HEAT STRESS*

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The physiological adjustments of man to high environmental temperatures have been studied extensively in the adult. However, the influence of environmental temperature on the water and electrolyte balance of infants has not been adequately determined. This paper reports the changes in the distribution of body water and electrolyte which occurred in infants exposed to heat stress. Accurate balances were assured by the determination of skin losses.

The most striking result of exposure to high environmental temperatures is the production of sweat. Adolph[2] has summarized most of the work on this subject and has shown that the volume of sweat is proportional to the heat load. The concentration of sodium and chloride in the sweat of unacclimatized adults has been determined by many workers.[3, 16, 19, 21, 25, 26, 46, 47, 49] The reported concentrations vary from 10 to 140 mM per liter. The higher values may be erroneous because of evaporation occurring during the collection of sweat. Johnson, Pitts, and Consolazio[26] have summarized the factors which may modify the electrolyte composition of sweat. Desoxycorticosterone acetate lowers the chloride concentration of the sweat in adults.[29] Similarly, adrenal cortical extract decreases the concentration of sodium and chloride and raises the concentration of potassium.[20, 35]

Although it is known that the sweat of infants contains electrolyte,[1] the exact concentrations have not been measured.

Under conditions in which there was probably little sweating, Romminger and Meyer[42] and Swanson and Iob[45] found an appreciable loss of electrolyte from the skin. The latter workers found significant amounts of potassium in the skin washings of infants under one year of age kept at room temperature of 78°F. while dressed in light clothing. Approximately 1.7 mM of potassium per day or 35 per cent of the apparent retentions, excluding

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sweat, were recovered from the skin of a three-month-old infant. Freyberg and Grant[23] found that approximately 14 per cent of the total sodium loss in adults occurred through the skin at environmental temperatures leading to minimal sweating. The use of clothing in these observations makes the complete absence of sweating uncertain.

In addition to the initiation of sweating, exposure to high environmental temperatures leads to changes in the distribution of body water. Barbour and others[4, 5] found hemodilution in animals exposed to heat. They postulated that the dilution of the blood was dependent on a movement of fluid from intracellular to extracellular spaces. Overman and Feldman[30] demonstrated a significant increase in the thiocyanate space of monkeys from 18.6 per cent of the body weight in winter to 24.7 per cent in summer. Plasma volume did not change significantly. Bazett *et al.*,[8] using the dye method, found an increase in the circulating plasma volume after exposure for four to five days to 91°F. Although the incidence and severity of edema has been said to be greater during hot weather than cold, Conley and Nickerson[11] noted no significant increase in the volume of the extracellular fluid compartment of three normal adults at 80°F. as compared with 60°F. The wearing of clothes in this experiment may have modified the results since the effective environmental temperature is difficult to evaluate when clothing is used. Furthermore, it is unfortunate that 80° was chosen as the high temperature, since there is little heat stress at this temperature except during increased activity. However, Spealman *et al.*[44] were able to show some retention of water in the heat as manifested by weight gain. Despite much research on acute exposure to heat, there are limited data on the change in body water and electrolyte composition during chronic exposure to high environmental temperatures, especially in infants.

In the present study, eight complete balances were performed on three normal male babies exposed to environmental temperatures of 81° and 91°F. with relative humidities of 20 to 30 per cent. Their ages ranged from five to sixteen months. The data represent accurate determinations of body weight and intake and output, including separate collections of urine, stools, and skin washings performed in successive periods at controlled temperatures. Water loss by way of the lungs and skin was calculated according to the methods of Newburgh and Johnson[28, 27] and is fairly exact. However, the calculation of sweat volume is subject to some error. It was calculated from the actual evaporative water loss at 91° minus the calculated insensible water loss for that period.

The following equations and assumptions were used in the calculation:

S V — Sweat Volume
E W — Evaporative water loss
I W — Insensible water loss
P W — Evaporative water loss from lungs
D W — Water lost by diffusion through skin
I W = P W + D W = 43 grams per 100 Calories metabolized[27, 40]
S V = E W — (P W + D W)

At 81° Fahrenheit it is known that:

(a) P W = ⅓ I W = ⅓ × 43 grams per 100 Calories[9]
(b) D W = ⅔ I W = ⅔ × 43 grams per 100 Calories

At 91° Fahrenheit in the absence of tachypnea[10] it was assumed that:

(a) P W = ⅓ × 43 grams per 100 Calories
(b) D W = ⅔ × 43 grams per 100 Calories

although actually the water lost by diffusion through the skin (D W) is less than this sum (⅔ × 43 grams per 100 Calories) since active sweating reduces the diffusion gradient of water through the skin.

If a high caloric expenditure is assumed, thereby giving high values to the evaporative water loss from the lungs and water lost by diffusion from the skin, the value for sweat volume (S V) becomes a minimal one. The reasons for assuming a high caloric expenditure will be discussed later. The errors involved in the calculation of sweat volume (S V) are mainly in the values for pulmonary evaporation (P W) and diffusion of water from the skin (D W). The total evaporative water loss (E W) depends almost entirely on accurate measurements of the intake, output, and body weight and is changed about one gram when the assumed caloric expenditure is altered by 10 Calories per kilogram of body weight per day. This change is due to the difference in the carbon dioxide and oxygen exchange occurring with a different metabolic mixture.

The electrolyte in the sweat was considered to be equal to the skin washings at 91° minus the washings at 81°F. The calculation of shifts of body water is according to the method of Darrow[17] and depends upon the assumption that chloride in large part remains extracellular.

Plan of study

At the beginning of each period of observation the subject was washed three times with distilled water, weighed to within one gram, and restrained without clothing on a metabolism mattress. The mattress was covered with Duran plastic and nylon sheets which previously had been freed of electrolyte. All urine voided was collected without catheterization by tubing and was weighed and analyzed daily. Toluene was used as a preservative. Stools were collected and weighed as soon as passed and subsequently analyzed.

A carmine red marker was used to identify the stools for each period. Food mixtures were weighed before and after feeding and aliquots were taken daily for analysis. Regurgitation and stool wipings were collected with weighed cotton and were accurately measured. The values for regurgitation and stool wipings were subtracted from the intake and added to the output respectively; however, they were almost always negligible. Body weight

TABLE 1

PLAN OF EXPERIMENTS

Experiment	*Period*	*Duration days*	*Room T. °F.*	*Intake*
A	1	4	82	½ SM and 10% DM #2; 80 Calories per 100 cc. water ad libitum.
	2	4	91	Same
	3	3	82	Same
B	1	3	83	EM, DM #2, Water; 78 Calories per 100 cc. No ad libitum water.
	2	3	91	Same
	3	4	81	Same
	4	3	91	Same plus DOCA 3 mg. I M daily.
C	1	4	91	EM, DM #1 (2% added NaCl), Water; 76 Cal. per 100 cc. No ad libitum water.
	2	5	81	Same
D	1	4	91	EM, DM #2, Water; 35 Calories per 100 cc. No ad libitum water.
	2	5	81	Same

was determined each day in order to calculate the evaporative water loss. At the end of an experimental period the subject was again washed three times with distilled water, and the washings were pooled with rinsings of the bedding and restraints. The pooled washings were then evaporated and analyzed. All analyses were performed by volumetric and gravimetric methods in common use in this laboratory.[50]

The plan of each experiment is shown in Table 1, and it can be noted that in Experiments A and D the diet contained large amounts of water. In

TABLE 2

DAILY SKIN LOSSES OF WATER AND ELECTROLYTE

Subject	Experiment	Period	Age mos.	Weight kg.	Room T. °F.	Evaporative Water gms.	Skin Na mEq.	Skin K mEq.	Skin Cl mEq.	Sweat vol. cc.	Sweat Concentration Na mEq./l.	Sweat Concentration K mEq./l.	Sweat Concentration Cl mEq./l.
H	A	1	7	8.1	81	337	0.9	1.0	0.9	32	..	..	..
		2	7	8.2	91	896	3.7	6.2	4.6	592	4.9	9.0	6.3
		3	7	8.1	82	390	1.7	1.7	1.9	129	..	..	..
G	B	1	7	7.9	83	382	1.8	1.9	1.9	124	..	..	..
		2	7	8.0	91	743	2.2	3.7	2.9	485	1.8	4.1	2.5
		3	7	7.9	81	322	1.3	1.7	1.7	69	..	..	..
		4	7	8.0	91	728	2.4	3.3	3.3	471	2.3	3.4	3.4
	C	1	10	8.8	91	774	3.1	3.7	3.7	396	3.1	3.7	3.7
		2	10	9.1	81	302	1.2	1.3	1.6	0	..	..	..
	D	1	12	9.0	91	798	4.8	4.0	5.2	529	5.9	4.7	6.1
		2	12	8.7	82	327	1.7	1.5	2.0	78	..	..	..
F	A	1	5	5.6	81	201	0.9	0.9	1.1	0	..	..	..
		2	5	5.8	91	566	2.1	3.6	3.2	340	5.6	10.0	8.2
		3	5	5.7	82	231	0.9	0.8	1.1	0	..	..	..
	B	1	11	9.2	83	391	1.6	1.6	2.0	133	..	..	..
		2	11	9.2	91	723	2.8	3.8	3.7	464	4.1	5.6	4.3
		3	11	9.1	81	293	0.9	1.2	1.7	35	..	..	..
		4	11	9.2	91	698	2.5	3.4	4.4	440	5.7	7.7	6.4
	C	1	14	9.5	91	759	4.1	3.3	5.9	381	7.6	5.2	11.3
		2	14	9.6	81	258	1.2	1.3	1.6	0	..	..	..
	D	1	16	9.7	91	892	5.6	3.4	6.8	624	7.2	4.3	8.8
		2	16	9.7	82	342	1.1	0.7	1.3	97	..	..	..

Experiment B the intake of water was moderate, and in Experiment C a diet similar to B was supplemented with one gram of sodium chloride per day.

Results

At 81°F., there was a fairly constant loss of electrolyte from the skin (Table 2). The evaporation of water from the lungs and skin under these conditions varied somewhat from day to day but was roughly proportional to the degree of activity and to the size of the infants.

TABLE 3

DIRECT DETERMINATION OF CONCENTRATION OF CHLORIDE IN SWEAT

Subject	*Collection Time hrs.*	*Area sq. cm.*	*Sweat gms.*	*Cl Conc. mM/l.*
F	1.5	40.6	.4195	18.1
G	1.5	36.3	.3042	4.9
F	1.0	40.6	.3579	7.0
G	1.0	36.3	.2755	8.2
F	1.0	40.6	.2723	9.2
G	1.0	36.3	.1460	12.0
F	1.0	40.6	.3333	11.2
G	1.0	36.3	.1727	4.4

As could be expected, on raising the environmental temperature to 91° there was an immediate increase in the evaporative water losses and a three to fivefold increase in the excretion of electrolyte by way of the skin with the onset of active sweating. The calculated sweat volume was roughly 45 to 65 cc. per kilogram of body weight per day.

The concentration of sodium in the sweat ranged from 1.8 to 7.6 mM per liter, and the average of ten experimental periods was 4.8 mM per liter (Table 2). The potassium concentrations in the sweat varied from 3.4 to 10.0 mM per liter and averaged 5.8 mM per liter. The concentration of chloride was somewhat higher than that of sodium and ranged from 2.5 to 11.3 mM per liter, and the average was 6.1 mM per liter.

Determination of the concentration of chloride in sweat collected directly from a covered area on the abdomen of these infants revealed values of the same order of magnitude as those calculated from the balance data and are quite consistently low, averaging 9.4 mM per liter of sweat (Table 3). The direct analysis of sweat may be high in some cases because of the possibility

of evaporation during collection—the only likely error of the sampling. The values calculated from the balance data are also likely to be high because the calculated sweat volume is probably minimal. The administration of desoxycorticosterone acetate produced little change in the concentration of sodium, potassium, or chloride in the sweat. Moreover, the administration of supplemental sodium chloride produced no significant changes in these electrolyte concentrations in the sweat, even though the serum chloride concentrations were increased.

At 81°F. before exposure to heat, there was little change in the water and electrolyte content of the body. In two such control periods there were essentially negligible retentions of sodium and chloride and potassium when corrected for the balance of nitrogen* (Tables 4 and 5).

When the environmental temperature was raised to 91°F. with a relative humidity of 30 to 40 per cent, chloride was usually retained in the body. The retention of chloride was 4.6 mM per day on a milk mixture containing one-half skimmed milk, 10 per cent sugar, and providing 80 Calories per 100 cc., with supplemental ad libitum distilled water (Table 4). The retention of sodium at the same time was somewhat less than the chloride retention and amounted to 3.6 mM per day. There was little change in the potassium content of the body, but there was a greater retention of calcium and phosphorus throughout this experiment than is usually found during growth.[48] These retentions cannot be explained unless they represent a temporary retention incident to a change in diet.

On an evaporated milk and sugar mixture containing 78 Calories per 100 cc., without ad libitum water, the babies retained larger amounts of chloride and sodium on exposure to a temperature of 91°F. (Table 5). The retention of chloride was about 8.6 mM per day, and the retention of sodium was about half as much. Since there was a slight loss of body weight during this time, there must have been a rise in the serum chloride concentration. However, serum analyses were not obtained. The administration of 3 mg. of desoxycorticosterone acetate intramuscularly each day on this feeding regime caused a slight increase in the retention of chloride over the previous hot period and a larger increase in the retention of sodium at the high environmental temperature. The retention of sodium and chloride seemed to result from a diminished renal excretion of these ions.

When the chloride concentration of the milk mixture ingested was increased to about 45 mM per liter by the addition of 1.0 gram of sodium chloride (in Dextromaltose #1, Mead Johnson Company) per day, a more

* One gram of nitrogen equals 3 mM of potassium.[24]

TABLE 4

BALANCE DATA IN EXPERIMENT A

	Body Wt. *gms.*	*Total* *gms.*	*Solids* *gms.*	*Water* *gms.*	*CHO* *gms.*	*Fat* *gms.*	*Prot.* *gms.*	*N* *gms.*	*Cl* *mEq.*	*Na* *mEq.*	*K* *mEq.*	*P* *mEq.*	*Ca* *mEq.*	*Water Change* *gms.*	*Evap. Water* *gms.*	*Calories Metab.* *Cal.*
Period I	9190															
3 D. 83°																
Urine		1169	26	1143				9.51	64.5	59.1	76.9	49.6				
Stools		135	24	111		9.9		1.27	1.5	0.9	6.3	16.9	51.2			
Skin		1	1					0.21	6.0	4.7	4.8	0.3	1.0			
Intake		2550	347	2203	177	83	84	13.41	70.8	56.6	102.5	68.8	68.8			
Balance	2	1245	296	949				2.42	—1.2	—8.1	14.5	2.0	16.6	2	1173	1800
Period II	9192															
3 D. 91°																
Urine		559	30	529				9.86	43.7	42.4	81.0	47.5				
Stools		155	29	126		13.9		1.43	1.8	0.8	7.7	19.9	63.3			
Skin		1	1					0.55	11.0	8.5	11.4	0.4	1.4			
Intake		2871	391	2480	200	94	89	14.24	82.2	63.2	112.0	77.4	79.6			
Balance	—94	2156	331	1825				2.40	25.7	11.5	11.9	9.6	14.9	—118	2170	1800
Period III	9098															
4 D. 81°																
Urine		1991	40	1951				14.98	101.4	80.6	117.1	68.8				
Stools		244	43	201		21.4		2.15	3.3	0.8	12.3	27.4	89.0			
Skin		1	1					0.26	6.9	3.7	4.9	0.9	1.1			
Intake		3598	489	3109	250	117	111	17.86	103.5	79.8	139.5	97.5	96.8			
Balance	90	1362	405	957				0.47	—8.1	—5.3	4.2	0.4	6.7	86	1171	2390

TABLE 5

BALANCE DATA IN EXPERIMENT B

	Body Wt. gms.	*Total* gms.	*Solids* gms.	*Water* gms.	*CHO* gms.	*Fat* gms.	*Prot.* gms.	*N* gms.	*Cl* mEq.	*Na* mEq.	*K* mEq.	*P* mEq.	*Ca* mEq.	*Water Change* gms.	*Evap. Water* gms.	*Calories Metab.* Cal.
Period I	8109															
3 D. 81°																
Urine		2748	41	2707				12.46	103.6	70.9	109.4	47.7				
Stools		335	39	296		10.4		2.53	4.2	4.0	17.2	40.5	92.0			
Skin		1	1					0.16	3.7	3.4	3.8	0.6	0.9			
Intake		4784	744	4040	560	67	106	17.05	112.0	83.6	13.8	107.0	119.0			
Balance	118	1700	663	1037				1.90	0.5	5.3	7.4	18.2	26.1	112	1351	3080
Period II	8227															
3 D. 91°																
Urine		754	25	729				8.81	59.6	43.3	70.7	37.5				
Stools		348	29	319		6.1		2.48	3.7	1.2	16.8	31.0	63.9			
Skin		1	1					0.91	18.5	14.7	24.9	2.8	3.9			
Intake		4929	675	4254	512	61	94	15.00	100.2	76.2	120.7	98.0	102.6			
Balance	35	3826	620	3206				2.80	18.4	15.0	8.3	27.7	34.8	41	3585	3080
Period III	8262															
4 D. 81°																
Urine		1310	19	1292				7.02	63.6	44.2	55.6	28.7				
Stools		264	29	235		9.1		1.87	4.8	1.3	13.1	20.4	54.6			
Skin		1	1					0.29	6.3	5.1	5.8	1.4				
Intake		2680	431	2249	313	37	62	9.99	65.1	49.7	73.6	58.2	67.4			
Balance	—187	1106	383	722				0.81	—9.6	—0.9	—0.9	7.8	12.8	—136	1170	2350
Period IV	9188															
3 D. 91°																
Urine		591	30	561				10.01	35.1	33.8	79.0	46.5				
Stools		168	30	138		13.3		1.45	3.0	0.7	9.6	19.9	61.4			
Skin		1	1					0.50	13.5	7.4	10.3	0.5	2.6			
Intake		2838	386	2452	198	93	87	13.98	81.4	63.2	112.3	76.8	76.5			
Balance	—94	2078	325	1753				2.02	29.8	21.3	13.4	9.9	12.5	—111	2093	1800

severe disturbance of the electrolyte composition of the body occurred. The preformed water intake was about 100 to 105 cc. per kilogram of body weight per day and the caloric intake was approximately 100 Calories per kilogram per day. In four days at 91° the infants retained from 35.7 to 48.4 mM of chloride. The corresponding sodium retentions were 18.5 mM and 24.2 mM (Tables 6 and 8). The retention of potassium during this time was not remarkable when corrected for the nitrogen retention.

Accompanying this retention of chloride and sodium was an increase in extracellular water amounting to as much as 0.36 kilograms or 15 per cent of the original volume (Tables 7 and 9). One-half of this gain consisted of water which had moved from the intracellular compartment. This increase in the extracellular space was inadequate to prevent a rise in the serum electrolyte concentration. The serum chloride concentration rose to as high as 111.2 mM per liter with a fall in serum bicarbonate to as low as 17.6 mM per liter. There was a shift of 34 mM of sodium from the intracellular to the extracellular compartments, accompanying a movement of water from the cells. The urine chloride concentration was about 145 mM per liter, and the sum of the sodium and potassium concentrations in the urine was 285 mM per liter.

When a liberal water intake was assured by feeding a mixture containing only 35 Calories per 100 cc., there was no excessive retention of electrolyte at 91°F. In these experiments the water intake was about 160 cc. per kilogram per day, and the caloric intake was approximately 55 Calories per kilogram of body weight per day. The retention of chloride was less than 1.0 mM for four days in one baby, and the other baby had a negative balance of 7.4 mM of chloride (Tables 10 and 12). There was a negligible loss of sodium and a larger loss of potassium amounting to 7.0 mM when corrected for the nitrogen balance.

As could be predicted from the balance data, in this study there was little change in the serum electrolyte concentrations (Tables 11 and 13). The bicarbonate fell to 19.5 mM per liter, but the chloride did not rise at any time. There was a loss of water from the intracellular phase of 0.35 kilograms which accounted for most of the fall in body weight. This loss was about 10 per cent of the existing intracellular fluid volume. The extracellular volume was sustained with little change.

On lowering the environmental temperature there was a return toward a normal distribution of water and electrolyte in all the infants studied. In those experiments in which there had been a retention of chloride and sodium in the heat, there was a negative balance of these ions in the

TABLE 6

BALANCE DATA IN EXPERIMENT C

	Body Wt. gms.	*Total* gms.	*Solids* gms.	*Water* gms.	*CHO* gms.	*Fat* gms.	*Prot.* gms.	*N* gms.	*Cl* mEq.	*Na* mEq.	*K* mEq.	*P* mEq.	*Ca* mEq.	*Water Change* gms.	*Evap. Water* gms.	*Calories Metab.* Cal.
Period I	9527															
4 D. 91°																
Urine		821	48	773				13.62	115.5	109.8	113.2	65.4				
Stools		208	36	172		15		1.68	3.5	0.9	12.8	18.9	71.4			
Skin		1	1					0.50	23.6	16.5	13.4	0.4	2.1			
Intake		4436	720	3716	368	175	150	22.25	191.0	151.4	161.5	124.5	120.0			
Balance	113	3406	635	2771				6.45	48.4	24.2	22.1	39.8	46.5	95	3158	3800
Period II	9640															
5 D. 81°																
Urine		2211	59	2152				17.85	176.8	146.8	131.3	56.4				
Stools		336	43	293		21		1.92	4.1	1.1	3.4	32.6	95.5			
Skin		1	1					0.38	7.9	6.2	6.5	1.3	1.5			
Intake		3854	572	3282	292	140	119	17.70	166.7	134.4	131.7	102.5	98.6			
Balance	—95	1306	469	837				—2.45	—22.1	—19.7	—9.5	12.2	1.6	—91	1287	2850

TABLE 7

SERUM CONCENTRATIONS AND WATER AND ELECTROLYTE EXCHANGES IN EXPERIMENT C

	Serum Concentrations					*Water and Electrolyte Exchanges*					
Time	*Water* gms./l.	*HCO_3* mEq/l.	*Cl* mEq/l.	*Na* mEq/l.	*K* mEq/l.	*Change $(H_2O)_e$** gms.	*Change $(Na)_e$* mEq.	*Change $(K)_e$* mEq.	*Change $(H_2O)_i$** gms.	*Change $(Na)_i$* mEq.	*Change $(K)_i$†* mEq.
Control	933	23.8	100.4	139.2	5.4						
End of Period I	920	18.8	111.2	146.0	4.6	120	39.0	—1.1	—25	—15.0	3.7
End of Period II	928	22.1	107.6	140.0	5.0	—90	—29.0	0.3	0	9.3	—2.5

* Subscripts "e" and "i" refer to extracellular and intracellular respectively.

† Corrected for nitrogen retention.

TABLE 8

BALANCE DATA IN EXPERIMENT C

	Body Wt. gms.	*Total* gms.	*Solids* gms.	*Water* gms.	*CHO* gms.	*Fat* gms.	*Prot.* gms.	*N* gms.	*Cl* mEq.	*Na* mEq.	*K* mEq.	*P* mEq.	*Ca* mEq.	*Water Change* gms.	*Evap. Water* gms.	*Calories Metab.* Cal.
Period I	8818															
4 D. 91°																
Urine		865	36	829				13.91	142.5	123.0	132.0	54.7				
Stools		160	38	122		17		2.00	2.0	0.5	6.7	40.8	92.0			
Skin		1	1					0.57	14.8	12.5	14.7	1.1	1.6			
Intake		4457	770	3787	394	188	161	22.70	195.0	154.5	165.0	127.0	122.5			
Balance	284	3531	695	2836				6.22	35.7	18.5	11.6	30.4	28.9	180	3097	3500
Period II	9102															
5 D. 81°																
Urine		2486	38	2448				17.96	195.5	158.8	151.1	68.0				
Stools		247	41	206		15		2.09	2.7	1.5	7.7	41.9	96.0			
Skin		1	1					0.52	9.9	8.3	7.7	0.1	1.4			
Intake		4269	648	3621	330	158	135	20.05	189.0	152.1	149.1	116.0	111.9			
Balance	—102	1535	568	967				—0.52	—19.1	—16.2	—17.4	5.0	14.5	—101	1512	3520

TABLE 9

SERUM CONCENTRATIONS AND WATER AND ELECTROLYTE EXCHANGES IN EXPERIMENT C

	Serum Concentrations					*Water and Electrolyte Exchanges*					
Time	*Water* gms./l.	*HCO_3* mEq/l.	*Cl* mEq/l.	*Na* mEq/l.	*K* mEq/l.	*Change $(H_2O)_e$** gms.	*Change $(Na)_e$* mEq.	*Change $(K)_e$* mEq.	*Change $(H_2O)_i$** gms.	*Change $(Na)_i$* mEq.	*Change $(K)_i$†* mEq.
Control	930	20.2	100.4	140.1	4.6						
End of Period I	932	17.6	110.0	141.0	4.9	360	53.0	2.2	—180	—34.0	—10.0
End of Period II	932	23.0	101.6	140.0	4.6	—250	—40.0	—0.2	149	24.0	—15.7

* Subscripts "e" and "i" refer to extracellular and intracellular respectively.

† Corrected for nitrogen retention.

† Corrected for nitrogen retention.

TABLE 10

BALANCE DATA IN EXPERIMENT D

	Body Wt. gms.	*Total* gms.	*Solids* gms.	*Water* gms.	*CHO* gms.	*Fat* gms.	*Prot.* gms.	*N* gms.	*Cl* mEq.	*Na* mEq.	*K* mEq.	*P* mEq.	*Ca* mEq.	*Water Change* gms.	*Evap. Water* gms.	*Calories Metab.* Cal.
Period I	9775															
4 D. 91°																
Urine		3162	33	3129				11.46	50.6	48.0	82.5	48.2	46.2			
Stools		102	21	81		8		1.18	1.4	0.2	5.6	19.2	46.2			
Skin		1	1					0.38	27.2	22.5	13.4	0.5	0.9			
Intake		6490	383	6107	196	94	80	11.71	79.8	69.2	90.6	75.1	68.5			
Balance	—446	3225	328	2897				—1.31	0.6	—1.5	—10.9	7.1	21.4	—362	3569	2500
Period II	9344															
5 D. 81°																
Urine		6411	31	6380				15.64	97.5	78.5	120.5	61.2				
Stools		176	26	150		12		1.67	2.4	1.0	7.9	37.4	85.2			
Skin		1	1					0.26	6.5	5.3	5.0	0.6	1.1			
Intake		8782	518	8264	265	127	108	15.71	110.6	91.8	123.0	101.6	85.3			
Balance	378	2194	460	1734				—1.86	4.2	7.0	—10.4	2.4	—1.0	377	1712	2860

TABLE 11

SERUM CONCENTRATIONS AND WATER AND ELECTROLYTE EXCHANGES IN EXPERIMENT D

	Serum Concentrations					*Water and Electrolyte Exchanges*					
Time	*Water* gms./l.	*HCO_3* mEq/l.	*Cl* mEq/l.	*Na* mEq/l.	*K* mEq/l.	*Change $(H_2O)_e$** gms.	*Change $(Na)_e$* mEq.	*Change $(K)_e$* mEq.	*Change $(H_2O)_i$** gms.	*Change $(Na)_i$* mEq.	*Change $(K)_i$†* mEq.
Control	930	23.9	106.4	143.0	4.5						
End of Period I	927	19.5	106.0	143.1	4.9	—10	—4.0	0.7	—352	2.5	—6.3
End of Period II	929	21.6	104.4	136.3	4.0	70	—3.0	—1.5	307	10.0	—3.4

* Subscripts "e" and "i" refer to extracellular and intracellular respectively.

† Corrected for nitrogen retention.

TABLE 12

BALANCE DATA IN EXPERIMENT D

	Body Wt. *gms.*	*Total* *gms.*	*Solids* *gms.*	*Water* *gms.*	*CHO* *gms.*	*Fat* *gms.*	*Prot.* *gms.*	*N* *gms.*	*Cl* *mEq.*	*Na* *mEq.*	*K* *mEq.*	*P* *mEq.*	*Ca* *mEq.*	*Water Change* *gms.*	*Evap. Water* *gms.*	*Calories Metab.* *Cal.*
Period I	8965															
4 D. 91°																
Urine		3263	23	3213				9.35	63.4	52.9	70.0	42.1				
Stools		90	20	70		7		1.07	0.9	0.3	4.1	19.5	39.2			
Skin		1	1					0.78	20.9	19.0	16.1	0.3	1.0			
Intake		6324	373	5951	191	91	78	11.41	77.8	67.4	88.3	73.2	66.7			
Balance	—262	2997	329	2668				0.21	—7.4	—4.8	—1.9	11.3	26.5	—212	3190	2500
Period II	8688															
5 D. 81°																
Urine		6799	30	6769				14.50	78.3	68.8	100.9	53.7				
Stools		114	27	87		8		1.48	1.4	0.5	7.3	35.2	63.7			
Skin		1	1					0.30	9.9	8.3	7.7	0.1	1.4			
Intake		8837	521	8316	267	127	109	15.80	111.2	92.2	123.5	102.1	85.8			
Balance	182	1923	463	1460				—0.48	21.6	14.6	7.6	13.1	20.7	185	1638	2900

TABLE 13

SERUM CONCENTRATIONS AND WATER AND ELECTROLYTE EXCHANGES IN EXPERIMENT D

	Serum Concentrations					*Water and Electrolyte Exchanges*					
Time	*Water* *gms./l.*	*HCO_3* *mEq/l.*	*Cl* *mEq/l.*	*Na* *mEq/l.*	*K* *mEq/l.*	*Change* *$(H_2O)_e$** *gms.*	*Change* *$(Na)_e$* *mEq.*	*Change* *$(K)_e$* *mEq.*	*Change* *$(H_2O)_i$** *gms.*	*Change* *$(Na)_i$* *mEq.*	*Change* *$(K)_i$†* *mEq.*
Control	928	23.7	106.0	139.4	5.2						
End of Period I	929	20.2	104.0	141.1	4.5	0	3.0	—1.2	—212	—7.0	—1.7
End of Period II	931	23.3	100.8	137.6	5.0	250	26.0	1.9	—75	—1.4	7.1

* Subscripts "e" and "i" refer to extracellular and intracellular respectively.

† Corrected for nitrogen retention.

recovery period amounting to as much as 4.4 mM per day of chloride and somewhat less of sodium (Tables 3, 4, 5, 6, 8). Similarly, when there had been storage of extracellular water in the heat, there was a loss of this water at 81°F. (Tables 6 and 8). The serum electrolyte concentrations returned toward normal values during the recovery period (Tables 7 and 9).

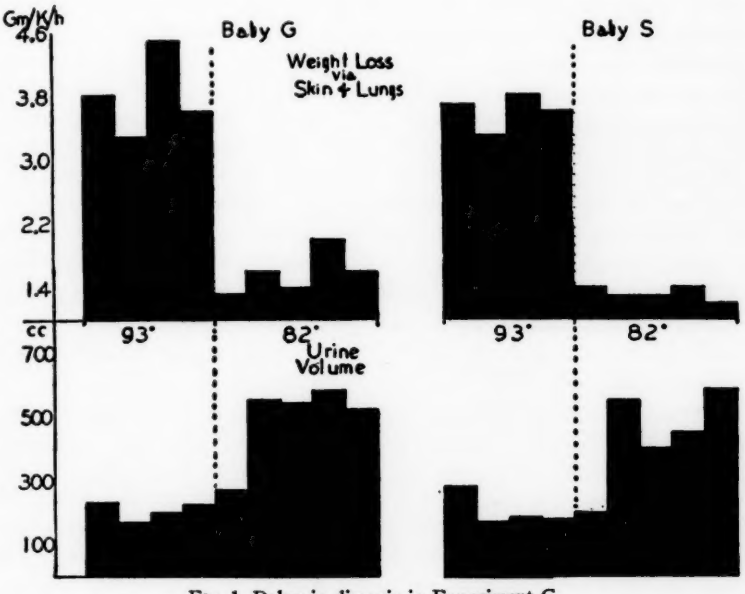

FIG. 1. Delay in diuresis in Experiment C.

In the experiment in which a dilute feeding mixture was used, one infant in the cool period replaced the deficit of intracellular water acquired at 91°F. (Table 11). The other infant replaced the debt of total body water but did not replenish the intracellular deficit (Table 13).

In the babies developing high serum chloride concentrations at 91° F., (Experiment C) the urine output was only 209 grams during the first 24 hours after reducing the environmental temperature despite a marked decrease in the extrarenal loss of water and an expanded extracellular volume (Fig. 1). The chloride concentration of this urine was 165 mM per liter. In contrast, in all of the other experiments (A, B, and D) in which the retention of sodium and chloride was considerably less, there was

† Corrected for nitrogen retention.

an immediate increase in the urine flow on lowering the environmental temperature. The mechanism of the observed delay in diuresis is not clear.

Since a change in the assumed caloric production alters the calculated water balance by the change in solids burned,[40] the assumption of a high caloric production at 91° F. increases the calculated water balance. This higher water balance fits the observed weight change at 91° F. better than values obtained by the measured insensible weight loss at 81° F. Unfortunately, facilities were not available for direct calorimetry, and indirect calorimetry is not practicable with infants of this age. However, the assumption of an increased metabolic rate in the heat is probably correct since rectal temperatures as high as 104° F. were noted in the study in which large sodium and chloride retentions were found. In the study in which a dilute feeding mixture was used to insure suitable water intake, there was no rise in rectal temperature above 100.5° F. However, the assumption of a slightly elevated caloric expenditure at 91° F. in this study seems justified, because an increase in skin temperature with a diminished temperature gradient between the skin and rectum would result in a mass of tissue functioning at a slightly elevated mean temperature.

Discussion

The use of skin washings in the determination of electrolyte balance increases the accuracy in the estimation of shifts of water and electrolyte. The data presented demonstrate that appreciable amounts of sodium, potassium, and chloride are lost through the skin at environmental temperatures of 81° F. in the absence of clothing. The values obtained in these studies are of the same order of magnitude as those reported by Swanson and Iob.[45] They represent a significant part of the electrolyte balance. In order to keep these losses constant and minimal, metabolic experiments should be carried out at 80° F. without clothing. At this temperature the subject is comfortable while at rest and the use of clothing or blankets may lead to sweating. When sweating occurs, the losses of water and electrolyte are markedly increased and must be measured by the collection of skin washings.

The concentrations of sodium and chloride in the sweat of normal babies were found to be one-fifth to one-tenth of the accepted values for unacclimatized adults. The concentration of sodium as determined from an average of ten experimental periods was 4.8 mM per liter of sweat. The concentration of potassium as determined from an average of these same periods was 5.8 mM per liter and is in the range of adult values. The ratio of

sodium to potassium in the sweat of these infants was usually less than 1.0 in contrast to ratios in the sweat of adults of 4.0 or 10.0 to 1.0.[47] The chloride concentration was determined by two different methods. The average concentration of chloride in the sweat collected directly from the skin, with precautions against evaporation, in eight, hourly periods was 9.4 mM per liter. This directly determined concentration agrees fairly well with the calculated concentration.

The potassium found in the skin washings during the warm period is probably present in actively secreted sweat rather than as a result of desquamation. The reason for this conclusion is that the skin washings in the recovery period at 81° F. contained much more desquamated epithelium and considerably less potassium.

The administration of desoxycorticosterone acetate did not lower the sodium or chloride concentration in the sweat nor did it raise the potassium concentration. These results could be predicted from the fact that the sweat concentrations of chloride and sodium already were extremely low. Presumably a maximal effect of adrenal hormones had already been obtained in these subjects.[12] The administration of supplementary sodium chloride in Experiment C did not appreciably increase the concentration of either ion in the sweat despite an increase in the serum chloride concentration.

The concentrations of electrolyte in the sweat which were determined in these experiments may not be the same as those of sick infants. In a previous study,[18] it was assumed that the sweat concentration of sodium and chloride was 40 to 60 mM per liter in infants sick with diarrhea and dehydration. These values were assumed because they fitted the other balance data and agreed with the concentrations obtained in adults by other observers. Balance studies on sick babies which include skin washings are needed to determine the actual sweat concentrations under these circumstances. Conn[13, 14, 15] found high concentrations of sodium in sweat in adrenal insufficiency and low concentrations in conditions associated with increased production of adrenocortical hormone or following injection of adrenocorticotrophic hormone. These findings suggest that in the presence of possible insufficient adrenal cortical function resulting from disease, the sweat glands may be unable to elaborate as hypotonic a secretion of sodium chloride as that from normal infants.

Since the insensible water loss per kilogram of body weight under nonsweating conditions is proportional to caloric expenditure[30] it was quite constant for each experimental period and tended to fall with increasing age and weight. The rough calculation of the total metabolism from the insensi-

ble water loss measured in a twenty-four-hour period is a possibly useful clinical method if a balance is available which can weigh to 1.0 gram.[21] The calculation is only valid when there is no sweating or hyperpnea.

The total evaporative water loss at 91° F. ranged from 80 to 110 grams per kilogram of body weight per day, or in terms of caloric expenditure, 95 to 140 grams per 100 Calories metabolized. The evaporation of water was obviously inadequate in the study in which supplemental sodium chloride was administered (Experiment C) because rectal temperature as high as 104° F. was noted, which rapidly fell on lowering the environmental temperature.

The evaporative water loss of each baby in the study in which a dilute feeding mixture was used (Experiment D) was higher than in Experiment C when calculated according to body weight or to caloric production. Using 0.58 Calories as the heat of vaporization of water it can be calculated that heat amounting to 58 Calories was lost by one baby on the dilute feeding mixture in excess of his evaporative water loss in Experiment C. Similarly, the evaporative loss of heat in the other baby in Experiment D in excess of his loss in C amounted to 240 Calories. This greater heat loss by the evaporation of water from the skin and lungs probably accounted for the preservation of normal body temperature in the experiments in which a large intake of water was assured (Experiment D). If the calculated sweat volumes are reasonably correct, the production of sweat per day in one baby increased from 396 grams in Experiment C to 529 grams in Experiment D. In the other baby studied, sweat production increased from 381 grams in Experiment C to 624 grams in Experiment D.

It is not clear why the evaporative water loss in Experiment C was inadequate to maintain a normal body temperature. Barbour[7] postulated that hemodilution had to occur before sweating was initiated. In Experiment C the electrolyte concentration in the serum was elevated in the warm period, and this fact might explain the low sweat volume. These findings are consistent with those of Barbour and Gilman[5, 6] on experimental animals and with those of Ginandes and Topper[20] on children. These workers consistently found depression in the insensible perspiration with the administration of sodium chloride and elevation of the serum osmotic pressure. The greater caloric intake in Experiment C also may have contributed to the rise in body temperature because of the greater heat load resulting from the specific dynamic action of the food ingested.

The four experimental periods in which serum concentrations were determined revealed two paradoxical types of response. First, when the

water intake was somewhat low, at 91° F. there was retention of sodium and chloride, increase in the concentration of electrolyte in the serum and expansion of the extracellular volume with resulting weight gain. The retention of chloride and sodium was apparently dependent on reduction of urinary excretion of these ions despite an increase in urinary concentration. It is not clear why the kidneys failed to excrete as much sodium and chloride as was necessary to preserve normal extracellular concentration, despite a normal or increased volume of extracellular water. The excretion of more water and electrolyte was not limited by the total osmolar concentration of the urine since an ultrafiltrate of serum would have reduced the urinary concentration. The experiments of Rehburg[41] may be pertinent to these findings and more recent work by Pitts and his co-workers,[32] and Smith *et al.*,[45] suggest that if a reduction in glomerular filtration had taken place in the heat, an excessive amount of sodium chloride would be reabsorbed by the kidney tubules if the tubular reabsorption of sodium chloride continued at the same rate. If the glomerular filtration had remained constant, the retention of sodium and chloride could be explained by an increased tubular reabsorption of these ions under the influence of the adrenal cortex. However, the determination of urinary 17-ketosteroids by Dr. Francis O. Humm of the Department of Pharmacology, Yale University School of Medicine, revealed no significant changes during the warm period. Sweat corticosteroids were not determined.[46]

The second type of response to heat was even more unexpected. When the water intake was high, the sodium and chloride content of the body remained about constant, and there was no change in serum concentrations. However, there was some loss of body water from the intracellular compartment while extracellular volume was preserved. Under these circumstances the urinary concentrations remained low and urinary excretion of sodium and chloride was adequate. Possibly a diminished rate of reabsorption of sodium and chloride was associated with the increased minute volume. The work of McCance and associates[33, 34, 51, 52] indicates that the urinary excretion of urea and electrolytes is greater when the daily urinary volume is high.

The data obtained from these experiments suggest certain practical considerations of value in the care of infants in summer. The use of dilute feeding mixtures or the administration of water ad libitum seems indicated in the heat. Clinically, the infants did not tolerate the heat well in the study in which water intake was moderate (Experiment C). Despite a gain of 2.5 per cent in body weight the infants had signs usually attributed to

dehydration. They were irritable, feverish, thirsty, and had dry mucous membranes.

When the infants were given large amounts of water (Experiment D) they had few symptoms of dehydration despite a loss of 4 to 5 per cent of the body weight in the warm period. They appeared happy and had no significant elevation of rectal temperature.

The data indicate that the use of supplementary sodium and chloride for normal infants in hot weather is not necessary. The concentration of sodium and chloride in the sweat of infants is much lower than in the sweat of adults. Therefore, the loss of sodium chloride in hot weather is small in infants, in relation to the loss of water by evaporation, and can be replaced by the usual milk mixtures without added sodium chloride. The excessive intake of sodium chloride in the presence of reduced urine flow can lead to hyperosmolarity of the extracellular fluid, thereby, possibly interfering with the evaporative loss of water from the body.

Summary and conclusions

The balance of water and electrolyte was obtained in four infants at 81° and 91° F. Skin washings were determined in all the studies. In four studies serum concentrations at the beginning and end of the balance periods were also obtained. The average sweat concentrations of sodium and chloride of normal infants were found to be low, 4.8 mM and 6.1 mM per liter respectively. The potassium concentration was 5.8 mM per liter.

Under conditions which lead to minimal or no sweating, appreciable amounts of sodium, chloride, and potassium are lost from the skin, 1.0 mM, 1.4 mM, and 1.1 mM per day respectively; and skin washings are necessary for accurate balances of electrolyte.

When the food does not contain abundant water, high temperature leads to an increase in body water, sodium, and chloride. Extracellular volume and concentrations are increased and slight acidosis develops. This change in body composition depends on failure of the kidneys to excrete sodium and chloride and water.

However, when abundant water is available, high environmental temperature does not lead to a retention of water, sodium, or chloride and tolerance to heat seems to be increased.

The changes in body water and electrolyte accompanying changes in environmental temperature are so great that environmental temperature should be rigidly controlled in all metabolic studies.

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GAS EXCHANGE IN THE LUNG DEPRIVED OF PULMONARY ARTERIAL SUPPLY*

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Upon ligation of the left branch of the pulmonary artery in the dog, there is exposed to the gases in the alveoli of this side a capillary bed supplied solely by systemic arterial blood. In such a lung, blood from the bronchial arteries has been demonstrated to gain direct access to the capillaries of the alveoli through large pre-capillary anastomoses that develop with branches of the pulmonary arteries which remain patent despite the ligature at the proximal end.[7] As the collateral circulation expands, the bronchial vessels carry a flow enormously greater than the normal—equal in volume at the end of eighteen months to approximately one-third of the output of the right ventricle.[3] The burden of this flow falls solely upon the left side of the heart whose output exceeds that of the right by an amount equal to that of the collateral. The situation is analogous to that of an arterio-venous fistula—systemic artery to pulmonary vein.

Not only does this blood maintain the structural integrity of the parenchyma of the left lung, but when not fully saturated, it can also function in the absorption of oxygen. Thus a lung deprived of its pulmonary arterial supply may still possess respiratory function. The observations reported here consider some quantitative aspects of the exchange of gases between such a capillary bed and the alveoli. Two studies,[5, 12] each of a single patient, have recently appeared, but there has not been published, to our knowledge, a detailed experimental investigation.

The observations to be reported were made on dogs under sodium pentobarbital anesthesia under four conditions: (A) Both lungs supplied with room air; (B) as in A, but exchange across the carina at the tracheal bifurcation interrupted by means of a bronchospirometric cannula; (C) right lung supplied with room air, bronchospirometric cannula in place, and left lung re-breathing into a spirometer or rubber bag; (D), as in C, but right lung connected to a spirometer containing oxygen.

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Methods

The animals were prepared by ligating the left pulmonary artery in each instance by a method previously described.[2] Subsequent procedures were carried out under sodium pentobarbital (35 mg/kg) anesthesia. Gases from the depths of the bronchial tree were obtained by intubation, according to a technique employed by Birath,[1] and before him by Loewy and Schrötter,[9] and by Krogh.[6] As in Birath's method, ureteral catheters (No. 6 or 8 French) were passed into the basal bronchi of each lung either under direct bronchoscopic observation or through the two halves of the tracheal divider. Gases were aspirated repeatedly, approximately 1 cc. at the end of each expiration, through the catheters into mercury-filled storage bulbs until adequate samples were collected for analysis.

The tracheal divider used for isolating the respiratory exchange of each lung is a VanAllen cannula modified for bronchospirometry.[2, 13] This cannula was also used in the rebreathing experiments (conditions C and D), in which the left lung was connected to a recording spirometer or a rubber bag, as desired, while the right was in communication with room air or a supply or oxygen.

Oxygen tensions were determined by the method of Fasciolo and Chiodi,[4] employing a special type of tube which permits the rapid chilling and centrifugation of blood and subsequent harvesting of plasma without exposure to the atmosphere. It was necessary to effect rapid separation of the plasma to minimize the consumption of oxygen by the cells of the blood.

Analyses of the blood or plasma were done in the VanSlyke apparatus by standard methods, with the modifications for plasma oxygen introduced by Fasciolo and Chiodi.[4] Analyses of gases were by the Henderson-Haldane technique. In all of these procedures duplicate analyses were required to check within 0.1 vol. %.

Observations

1. *Composition of gases in the basal bronchi.*

Determinations were made of the composition of end-expiratory gases drawn simultaneously from the deeper respiratory passages of the intact right lung and the left lung whose pulmonary artery had been ligated. Both lungs were in free communication with the outside air during this time. The samples obtained under free transcarinal exchange (condition A) are compared in Table 1 with those obtained with a tracheal divider in place (condition B). In considering the results of the analyses it must be remembered that since the animals were under sodium pentobarbital anesthesia deep enough for bronchospirometry, the arterial blood was unsaturated, averaging approximately 63% when both lungs were breathing air; in the conscious resting animals the arterial oxygen was invariably normal, and was 100% when the right lung was breathing oxygen even under the barbiturate. The reasons for the unsaturation in anesthesia with another barbiturate, sodium pentothal, have been discussed elsewhere.[10]

It is obvious from Table 1 that under both conditions the oxygen content of the basal bronchi in the intact lung is lower, and the CO_2 content higher, than in the left lung. When the CO_2 content in the left lung is low, the oxygen tends to be relatively high. Stated otherwise, the gas content of the left lung tends more to resemble room air than that of the right lung.

TABLE 1

COMPOSITION OF GASES IN BASAL BRONCHI

	Condition A						*Condition B*					
	Exp. #	*Time (mo.)*	*CO_2 Left*	*CO_2 Right*	*O_2 Left*	*O_2 Right*	*Exp. #*	*Time (mo.)*	*CO_2 Left*	*CO_2 Right*	*O_2 Left*	*O_2 Right*
					Dog 52							
	78	¼	3.1	5.8	18.1	14.9	78	¼	1.1	6.4	20.5	14.3
	86	1	4.1	6.9	16.9	10.8	84	¾	2.1	6.6	19.1	13.9
							89	1½	2.2	5.6	20.1	13.3
							143	5	3.2	5.0	19.2	11.6
Mean			3.6	6.4	17.5	12.9			2.2	6.1	19.2	13.3
					Dog 11							
	56	8¾	4.0	5.9	18.2	13.5	59	9	2.0	6.4	19.0	14.7
	65	9¾	6.3	7.2	15.0	11.9	67	10	5.1	6.8	16.8	12.2
Mean			5.2	6.6	16.4	12.7			3.6	6.6	17.9	13.5
					Dog 9							
	77	12¾	5.8	7.6	14.3	10.3	76	12½	4.4	5.9	17.7	12.1
	83	13¼	5.9	7.6	15.2	10.4	80	12¾	5.5	6.3	15.6	11.2
	85	13½	6.3	6.3	10.3	10.0	87	14	5.0	6.9	17.1	10.2
							90	14	6.2	6.8	12.9	10.0
Mean			6.0	7.2	13.3	10.2			5.2	6.5	15.8	10.9

NOTE: Time is given in months after ligation of the pulmonary artery. Composition of gases is given in volumes %.

This contrast with the gaseous contents of the right basal bronchi is even more striking when the tracheal divider is in place than when transcarinal exchange is free. Under the latter condition (A), the left lung takes in at each inspiration a relatively large portion of the tracheal and pharyngeal "dead space air," for the reason that the minute volume of gas exchange of this lung is relatively lower than that of the right. In a series of determinations on the three animals listed in Table 1 the tidal volume of

the left lung ranged from 28 to 35% of the total exchange. This "dead space air" at the end of expiration is more representative of the contents of the alveoli of the right lung.

In all of the samples from the side of ligation the CO_2 tends to approximate much more closely than the O_2 the respective levels from the normal right side. Roh and his co-workers point out that the probable mechanism involves not only the twenty to thirty times greater diffusibility of CO_2 in comparison with O_2, but also the high dissociation gradient for the carbonate.[12]

The sooner after ligation of the pulmonary artery the samples from the left side are obtained, the closer the similarity to room air, especially under

TABLE 2

pO_2 OF GASES IN BASAL BRONCHI AND SYSTEMIC ARTERIAL BLOOD

Dog	*Exp.*	*Time (mo.)*	*pO_2, mm. Hg.*		
			Right lung	*Left lung*	*Blood*
52	86*	1	76	119	41
52	89†	1½	95	144	30
9	87*	14	74	123	22

* Transcarinal exchange unimpeded (condition A).
† Through bronchospirometric cannula (condition B).

condition B (tracheal divider in place). Thus, in the earlier weeks after ligation, the quantity of CO_2 leaving and the oxygen entering the relatively small volume of bronchial arterial blood then perfusing the capillaries of the left lung is insignificant in comparison with the volume of gases exchanged at each breath. Evidence for this is found in the fact that the pO_2 of the systemic arterial blood is lower than that of the contents of the left basal bronchi. The arterial pO_2 is lower, by some 35 to 65 mm. Hg, than that even of the right lung (Table 2). It is the latter datum which suggests that systemic venous blood is traversing poorly ventilated alveoli and is being contributed relatively unchanged to the general stream entering the left auricle. Later (dogs 9 and 11), the gases from the two sides tend to be more closely similar in composition.

2. *The lung as a tonometer.*

When the lung with a capillary bed supplied solely by systemic arterial blood was placed into communication with a spirometer or bag containing air, its function as a tonometer could be studied. Observations were made

under these conditions: (a) when the relatively normal right lung was open to air (condition C), and (b) when this lung was supplied with oxygen (condition D).

A. Condition C: While the right lung was breathing freely from the room, the left was connected through its cannula either with a rubber bag or with a spirometer containing respectively 750 cc. and approximately 2000 cc. of air. The sequence of events during the earlier phases of such an experiment can be demonstrated graphically by projecting selected points from the spirometric tracing as ordinates on a graph and by indicating the composition of the gases at intervals. This has been done in Figures 1 and 2 for the data of Experiment 80 which may be used as an example. It is apparent that there is at first an increase in the total volume of the gaseous contents of the spirometer, accounted for chiefly by the excess of CO_2 and N_2 transferred into the spirometer over the oxygen absorbed during the same interval. After the first thirty minutes the concentration of N_2 and CO_2 remains relatively constant, while O_2 absorption continues with the result that the contents of the spirometer decrease in volume below that at the start of the experiment. In this particular instance, at the end of an hour, 195 cc. of O_2 has been absorbed from the spirometer while 29 cc. of CO_2 and 31 cc. of N_2 were transferred into it; this resulted in a decrease of 135 cc. in the total volume of the contents of the spirometer.

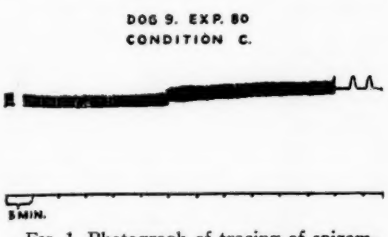

FIG. 1. Photograph of tracing of spirometer connected to the operated left lung while the right lung is breathing air. A fall in the curve indicates a rise in the volume of gases contained in the spirometer, and vice versa. The factors responsible for these changes are indicated in Figure 2. The sudden rise in the level of the tracing near the mid-portion of the curve results from withdrawal of a sample for analysis. At the right tracings during two respiratory cycles are shown with the kymograph at high speed.

The composition of the gases in the spirometer is recorded in Table 3. In the present experiment the percentage of oxygen at the end of an hour appears to be low in comparison with that of normal "alveolar air," but actually its tension is 82 mm. Hg, much higher than that of the arterial blood in any of the animals studied under similar circumstances of anesthesia (Table 2). Obviously equilibrium has not been attained at the

end of one hour. Inspection of the data shows that this must also be true for the other experiments recorded in Table 3.

B. Condition D: When the right lung is given O_2 rather than air to respire under similar circumstances, O_2 enters the left spirometer, more rapidly during the first thirty minutes as shown in Figures 3 and 4 constructed from the data of Experiment 80. CO_2 values are not indicated since this gas has been absorbed from the system by soda-lime scrubbers in the expiratory line of each spirometer. Even at the end of two hours in this experiment, the process of oxygen transfer has not ceased. It will further be noted from Figure 4 that N_2 is being absorbed from the left spirometer presumably to enter the right spirometer which contains nearly pure O_2 at the start. The rate of O_2 transfer into the left spirometer exceeds that of N_2 absorption, as a consequence of which the total volume of the gases is increased. At the end of two hours, the O_2 may reach a concentration of 39.8% and a tension of 286 mm. Hg (Table 4, Experiment 80, condition D). Figure 4 shows that during this interval the spirometer gained 445 cc. of oxygen (at ambient temperature and pressure), while losing 298 cc. of N_2; thus, the total gain in volume was 147 cc. The results of the various determinations are comparable in Dogs #9 and #11 both of which were tested more than eight months after ligation of the pulmonary artery. During

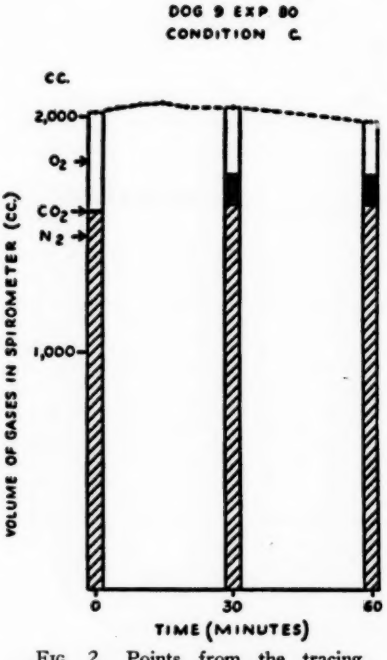

FIG. 2. Points from the tracing shown in Figure 1 have been used to indicate the total volume; in addition, the composition of gas samples obtained at three points is indicated. It is obvious that the early rise in total volume results from the excess of CO_2 and N_2 transferred into the spirometer over the O_2 absorbed, a condition that is reversed later. Numerical data are given in Table 3.

the first six weeks (Dog #52) the rise of O_2 appears to be much slower, but more quantitative data are needed to substantiate this point. The difference does not appear to be associated with the mean tidal volume as this is actually greater in Dog #52 than in either of the others (94 cc. for Dog #52, 93 cc. for Dog #11, and 79 cc. for Dog #9).

A comparison of the oxygen tensions in the arterial blood and in the contents of the left spirometer at the end of two hours is available for Dog #52, Experiments 86 and 89, one and one and one-half months after ligation of the left pulmonary artery respectively. In Experiment 86 the

TABLE 3

LUNG AS A TONOMETER: CONDITION C

Dog	*Exp.*	*Time (mos.)*	*Interval (min.)*	*CO_2 vol. %*	*O_2 vol. %*	*Container*	*Vol. at start, cc.*
	56	8¾	60	6.3	11.6	Bag	750
			75	6.9	11.7		
11	59	9	60	5.9	11.0	Bag	750
			75	6.8	10.7		
	62	9¼	60	7.7	10.6	Bag	750
			75	7.3	10.2		
9	80	12¾	30	6.4	13.9	Spirometer	2017
			60	6.5	11.4		

arterial oxygen tension was 391, while the pO_2 in the left lung was 171, and in Experiment 89, the respective pO_2 values were 405 and 189. In view of the low final percentages of oxygen reached at the end of two hours (Table 4), these large gradients are not surprising. Even at the end of 12¾ months in Dog #9, however, the oxygen tension in the left lung was only 286 mm. Hg when the oxygen percentage was 39.7, the highest recorded at the end of two hours in any of the present observations. Although data on the arterial pO_2 are not available in this instance, it is probable that a gradient of at least 100 mm. Hg existed.

Discussion

Common to all of these observations are the large differences between the alveolar and arterial pO_2 values, much greater than those which exist

normally, at least in man.[3, 8] In the case of the "normal" right lung these can be accounted for by the sodium pentobarbital anesthesia with the consequent poor ventilation of many alveoli which results in failure of oxygenation of considerable quantities of venous blood. Desaturation of the systemic arterial blood under another barbiturate has been demonstrated by Penrod and Hegnauer.[10]

More difficult to explain is the disequilibrium on the left side, where the pO_2 of rebreathed air is higher at the end of an hour than the arterial pO_2 when the normal lung is breathing air, and lower than arterial pO_2 when the right lung is breathing oxygen. These differences cannot be accounted for on the basis of shunting of blood. Among the factors that may be concerned, however, are (i) the relatively small flow through the lung whose pulmonary artery has been ligated; (ii) inadequate turnover of gases in the left spirometer or rebreathing bag; (iii) decreased permeability of the alveolar membranes[8, 11] after ligation of the pulmonary artery.

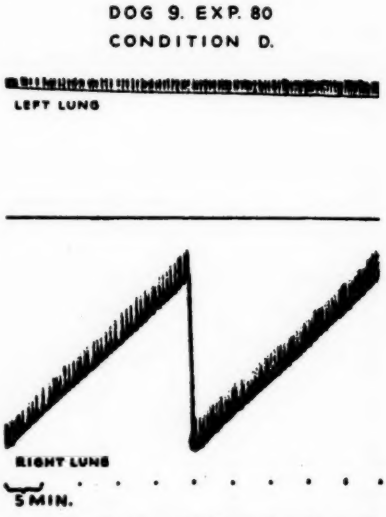

FIG. 3. Photograph of bronchospirometric tracing during the first fifty minutes while the left lung is rebreathing from the spirometer and the right is respiring oxygen. The fall in the upper tracing indicates a rise in the total volume. Alignment of portions of this curve with a straightedge shows that this increase is more rapid at first.

Concerning the first factor, data are available from previous observations on the bronchial arterial flow made on these animals under sodium pentobarbital anesthesia. During the first six weeks the expected flow through the alveoli of the left lung is usually less than 250 cc/min/M^2.[2] Thus the slow circulation is probably of importance so soon after ligation. After the eighth month, however, flows of more than 500 cc/min/M^2 are to be expected.

Concerning the second factor, the tidal volumes of the left lung of the three dogs, as averaged in each instance from a large series of observations

TABLE 4

LUNG AS A TONOMETER: CONDITION D

Dog	Exp.	Time (mos.)	Interval (min.)	CO_2 vol. %	O_2 vol. %	Container	Vol. at start, cc.
	86	1	30	0.0	21.9	Spirometer	2000
			126		24.2		
52	89	1½	38		23.0	Spirometer	2000
			127		26.6		
	59	9	60	8.5	24.4	Bag	750
			75	9.7	26.1		
	62	9¼	60	11.3	33.6	Bag	750
			75	10.9	36.1		
	64	9½	15	8.3	24.1	Bag	750
			30	8.5	26.8		
			120	7.5	36.0		
			180	7.9	36.4		
11	65	9¾	15	5.7	23.1	Bag	750
			30	7.1	25.8		
			60	7.2	31.2		
			120	6.9	37.9		
	68	10	30	7.1	23.4	Spirometer	2000
			60	9.0	26.1		
			120	11.3	29.2		
	69	10¼	30	9.4	22.4	Spirometer	2000
			120	9.9	27.2		
	75	12¼	30	0.0	24.2	Spirometer	2000
			60	0.0	26.6		
			90	0.0	28.5		
	76	12½	30	0.0	35.1	Spirometer	2000
			60	0.0	37.4		
	80	12¾	30	.07	33.8	Spirometer	2000
			60	.04	36.6		
9			120	.04	39.7		
	85	13½	30	0.1	30.3	Spirometer	2000
			60	0.1	33.0		
			120	0.1	37.2		
	87	14	30	0.02	25.6	Spirometer	2000
			111	0.00	33.1		
	90	14	152	0.0	33.9	Spirometer	2000

in many experiments, range from 76.6 to 82.4 cc. Thus, with a respiratory rate of 10, a volume corresponding to the entire contents of the spirometer should have been exchanged at least twenty times in an hour, and in the case of the rubber bag at least fifty times.

These considerations suggest that the alveoli of the lung with ligated pulmonary artery may not be as permeable to the passage of oxygen as those of the normal lung. No obvious histological differences have been observed, however.

Summary and conclusions

Under sodium pentobarbital anesthesia, the gases in the basal bronchi of a lung whose main pulmonary artery has been ligated as long as fifty weeks previously have a higher oxygen and lower CO_2 content than those in an intact lung. The difference is less striking the greater the interval after ligation; at all times the CO_2 shows proportionately less deviation than the O_2.

There is evidence from bronchial intubation experiments of considerable transcarinal exchange.

With a bronchospirometric cannula in place and the lung of the ligated side rebreathing, gaseous equilibrium with the systemic arterial blood in the latter is not attained on the operated side, even at the end of two hours, since there is evidence that oxygen transfer has not ceased.

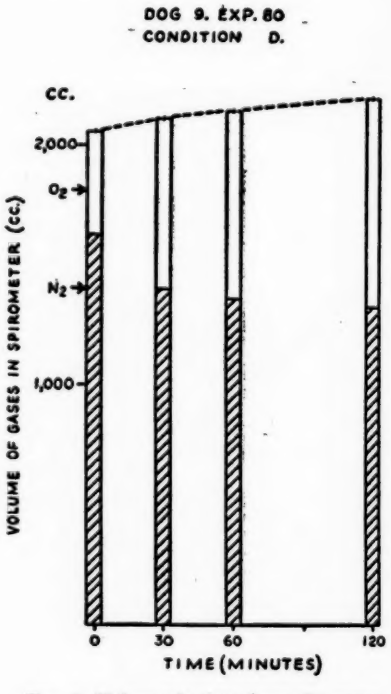

FIG. 4. Volumetric data from the upper tracing of Figure 3 are indicated here in relation to the composition of the gases. Percentage figures are given in Table 4. The rates of transfer of both O_2 and N_2, especially of the latter, are more rapid at first.

These observations suggest, with due allowance for the effect of barbiturate anesthesia and decreased tidal volume of the operated lung, that

the permeability of the alveolar membranes to gases may be impaired after ligation of the pulmonary artery.

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THE ROLE OF PROTEOLYTIC ENZYMES IN THE BIOSYNTHESIS OF PEPTIDE BONDS*

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Previous studies on the specificity and mode of action of the proteolytic enzymes have shown[4, 10] that these enzymes catalyze the rate of attainment of equilibrium in reactions that involve the hydrolysis or synthesis of peptide bonds†:

$$\mathrm{RCO\text{-}NHCHCO\text{-}NHR'' + H_2O \rightleftharpoons RCO\text{-}NHCHCOOH + NH_2R''}$$

(R′ on the CHCO side; R′ on the CHCOOH side)

In homogeneous systems, the equilibrium is far to the right, and the free energy change in the hydrolytic reaction is about —3000 calories per mole.[7] To effect peptide synthesis in the presence of a suitable catalyst, therefore, the reversal of hydrolysis must be coupled to an exergonic process. As pointed out elsewhere,[5] such a coupling may be achieved through the choice of reactants which yield a synthetic product whose solubility is less than its equilibrium concentration. At equilibrium a supersaturated solution of the synthetic product results, and the exergonic process of precipitation of the difficultly soluble product from the solution drives the peptide synthesis to a point at which the equilibrium concentrations of the reactants have been established. One of the first instances of the operation of such a coupled reaction in the case of protein-splitting enzymes was the demonstration by Bergmann and Fraenkel-Conrat[3] that the plant proteinase papain, following activation by cysteine, catalyzes the reaction:

$$\underset{\text{Benzoylglycine}}{\mathrm{C_6H_5CO\text{-}NHCH_2COOH}} + \underset{\text{Aniline}}{\mathrm{NH_2C_6H_5}} \rightarrow \underset{\text{Benzoylglycinanilide}}{\mathrm{C_6H_5CO\text{-}NHCH_2CO\text{-}NHC_6H_5}}$$

It is the purpose of this communication to call attention to another type of reaction catalyzed by proteolytic enzymes, first postulated by Bergmann and Fraenkel-Conrat,[3] and which involves the replacement of one participant in a peptide bond by another. Reactions of this type may be termed

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† In what follows, the term "peptide bond" will be applied to any CO-NH linkage in which either the carbonyl or imino group belongs to an amino acid residue.

"transpeptidation" or "transamidation" processes, by analogy with the usage of "transglycosidation" to designate the enzyme-catalyzed replacement of one participant in a glycosidic linkage by another.[9] A transpeptidation reaction may be formulated as follows:

$$\mathrm{RCO\text{-}NH\overset{R'}{\overset{|}{C}}HCO\text{-}NHR'' + NH_2R''' \rightleftharpoons RCO\text{-}NH\overset{R'}{\overset{|}{C}}HCO\text{-}NHR''' + NH_2R''}$$

In their study of the enzyme-catalyzed synthesis of benzoylglycinanilide from hippuric acid and aniline, Bergmann and Fraenkel-Conrat presented experimental evidence for the catalysis of a transpeptidation reaction. They found that the rate of formation of benzoylglycinanilide from benzoylglycinamide and aniline, in the presence of cysteine-activated papain, was somewhat more rapid than was the synthesis of the anilide from hippuric acid and aniline. Consequently, the free acid was unlikely as an intermediate in the transformation of the amide to the anilide.

It will be evident that, in contrast to the hydrolytic or synthetic processes, the over-all free energy change in a replacement reaction cannot be very great, since one may consider the energy of the peptide bond that is broken to be used for the synthesis of the new peptide bond that is formed, via a transient intermediate in which both amino groups are attached to the carbon atom of the carbonyl group forming the peptide bond:

$$\mathrm{R\text{-}\overset{O}{\overset{\|}{C}}\text{-}NHR' + NH_2R'' \rightleftharpoons \left[\begin{array}{c} OH \\ | \\ R\text{-}C\text{-}NHR' \\ | \\ NHR'' \end{array}\right] \rightleftharpoons R\text{-}\overset{O}{\overset{\|}{C}}\text{-}NHR'' + NH_2R'}$$

Consequently, it may be expected that such an enzyme-catalyzed replacement reaction should occur to an appreciable extent in homogeneous solution, without the necessity for the removal of the product of transpeptidation through insolubility, as in the case of the conversion of hippuric acid amide to the anilide. Accordingly, experiments were performed in which cysteine-activated papain was allowed to act on benzoylglycinamide in the presence of an equivalent quantity of isotopic ammonium-N, whose isotope concentration was 32.3 atom per cent excess N^{15}. The action of the enzyme was allowed to proceed until a significant portion of the amide had undergone enzymatic hydrolysis. If, during the incubation period, the enzyme had catalyzed the replacement of $—N^{14}H_2$ by $—N^{15}H_2$ in the amide bond, interruption of the hydrolysis prior to its completion, and isolation of a pure sample of the residual benzoylglycinamide, should have yielded a

product with a measurable isotope content. As will be seen from the data in Table 1, significant amounts of isotopic nitrogen were in fact incorporated into the substrate during the reaction.

The procedure employed may be illustrated by means of a description of a representative experiment: 445 mg. of benzoylglycinamide (2.5 mM)

TABLE 1

REPLACEMENT REACTIONS CATALYZED BY PAPAIN

Temperature, 38.1°C; pH 4.9-5.0; concentration of activator (cysteine), 0.004M; methanol, 0.3 cc. per cc. of test solution

Initial reactants	*Enzyme conc. (prot. N per cc. test sol.)*	*Hydrolysis of amide bond*		*Isolated amide*			*Per cent replacement**
				N content	*N^{15} conc.*		
					Cmpd.	*Amide-N*	
	mg.	*hrs.*	*%*	*%*	*atom % excess*	*atom % excess*	*%*
Benzoylglycinamide	0.28	5	32	15.66	0.075	0.150	0.46
(0.05 M)		19	50	15.76	0.102	0.204	0.63
$(NH_4)_2$Hcitrate† (0.025 M)		19	8‡	15.59	0.020	0.040	0.12
		19	0§	15.62	0.001	0.002	0.006
Carbobenzoxy-L-methion-	0.21	0.75	35	9.85	0.018	0.036	0.11
inamide (0.01 M)		2	76	9.85	0.042	0.084	0.26
$(NH_4)_2$Hcitrate† (0.005 M)		0.75	17‡	9.79	0.011	0.022	0.07

* $\frac{\text{Isotope concentration of amide-N}}{\text{Isotope concentration of ammonia-N added}} \times 100$

† Isotope concentration, 32.3 atom per cent excess N^{15}.

‡ No cysteine added.

§ No papain added.

were dissolved in 15 cc. of methanol, and 10 cc. of 0.125 M $(NH_4)_2$H citrate (containing 32.3 atom per cent excess N^{15}) were added. 2 cc. of 0.1 M cysteineHCl were then introduced, followed by 20 cc. of a solution of papain[11] containing 14 mg. of protein nitrogen, and the volume was adjusted to 50 cc. After an incubation period of 19 hours at 38.1° C, microtitration of a 0.2 cc. aliquot by the method of Grassmann and Heyde[12] showed that 50 per cent of the amide had been hydrolyzed by the enzyme. The solution was withdrawn from the water bath, poured into 500 cc. of cold 95 per cent ethanol, chilled in the refrigerator for 30 minutes, and the

precipitated protein was filtered off with the aid of analytical Filter-Cel. The filtrate was evaporated to dryness under reduced pressure (bath temperature, 40-50° C), and the residue was dissolved in 4 cc. of hot 2 N NH_4OH. The resulting solution was clarified by filtration, and the filtrate was chilled, whereupon benzoylglycinamide crystallized. The product was collected by filtration and subjected to a second crystallization from 4 cc. of hot 2 N NH_4 OH. After being dried at 78° C *in vacuo* over P_2O_5, the product (54.9 mg.) melted at 183° C, had a nitrogen content of 15.76 per cent (theory for benzoylglycinamide, 15.72 per cent nitrogen), and an isotope concentration of 0.102 atom per cent excess N^{15}. After an additional recrystallization from 2 cc. of hot NH_4OH, the isotope concentration was found to be 0.101 atom per cent excess, thus showing that constancy of isotope concentration had been achieved following two crystallizations of the amide from non-isotopic NH_4OH. The value of 0.102 atom per cent excess N^{15} corresponds to an isotope concentration of 0.204 atom per cent excess N^{15} for the amide-N, since the α-amino-N could not have been replaced by isotopic nitrogen under the conditions of this experiment. From the latter value, and the isotopic concentration of the ammonium citrate added at the start of the reaction, it may be calculated that 0.63 per cent of the isolated amide had been formed by a reaction with isotopic NH_4^+. This is indicated in Table 1 as "per cent replacement."

The other experimental data presented in Table 1 were obtained in a manner similar to that described above. The table also includes the results of control experiments in which either cysteine or papain was omitted. The slight hydrolysis observed in the absence of added activator was accompanied by a slight but significant incorporation of isotopic nitrogen, while in the absence of enzyme, where no hydrolysis took place, no uptake of isotope was noted.

In addition to the data on the incorporation of isotopic nitrogen into benzoylglycinamide, Table 1 includes the results of experiments (performed in collaboration with Mr. Sterling P. Taylor Jr.) on another substrate of papain, carbobenzoxy-L-methioninamide. This compound has been found[8] to be one of the most sensitive known substrates for papain, and its rapid hydrolysis (determined by measurement of ammonia liberation in Conway vessels) permitted the conduct of experiments of much shorter duration than in the case of benzoylglycinamide. Because of its insolubility, carbobenzoxy-L-methioninamide was present in 0.01 M concentration, and while an appreciable incorporation of isotope was found, the extent of isotope incorporation was less than that noted for the glycine-containing

substrate at a concentration of 0.05 M. Although further experiments are required to establish more definitely the quantitative relation between the extent of hydrolysis and the extent of transpeptidation, the data at hand strongly suggest that, under a given set of conditions, there is a direct proportionality between the molar quantity of amide hydrolyzed and the per cent replacement.

In evaluating the data in Table 1, it is important to calculate the extent of isotope incorporation to be expected if no replacement had occurred, but only enzyme-catalyzed synthesis from hippuric acid or carbobenzoxy-L-methionine (arising from the hydrolysis of the respective amides) and ammonia. Such a calculation may be made on the basis of the assumption that, under the conditions of these experiments, the free energy change in the synthetic process is +3000 calories per mole. This corresponds to an equilibrium constant K = [amide]/[acid][ammonia] of about 0.01. One may then estimate the concentration of the amide that would be in equilibrium with the maximal possible concentration of the acylamino acids. For example, if the concentration of hippuric acid and isotopic ammonia be taken at 0.05 M, it follows that, at equilibrium, the concentration of isotopic benzoylglycinamide would be 2.5×10^{-5} M. This would correspond to 0.05 per cent incorporation of isotopic nitrogen into the amide. Clearly, when the hydrolysis of the amide has proceeded only to about 50 per cent of completion, less hippuric acid is available for direct synthesis, and the extent of isotope incorporation by this route would be correspondingly smaller. Similarly, it may be calculated that in the experiments with carbobenzoxy-L-methioninamide, run at lower initial concentrations (0.01 M) of the reactants, the maximum possible incorporation of isotope through synthesis from carbobenzoxy-L-methionine and isotopic ammonia is about 0.01 per cent. Since these calculated values are far lower than those actually found, it may be concluded, therefore, that the enzyme-catalyzed incorporation of isotope into the acylamino acid amides was due to a replacement reaction.

These data clearly confirm the theory of Bergmann and Fraenkel-Conrat that proteolytic enzymes such as papain catalyze transpeptidation reactions. Recent data of Zamecnik and Frantz[16] show that the catalysis of transpeptidation reactions is not limited to protein-splitting enzymes such as papain, since these authors have demonstrated the ability of a crude dipeptidase preparation to cause the incorporation of radioactive glycine into glycylglycine during the enzymatic hydrolysis of the dipeptide. In view of these results, it is possible to conclude that the catalytic action of proteo-

lytic enzymes at a peptide bond lies in the activation of the carbon atom of the carbonyl group, with the transient addition of either OH (with ultimate hydrolysis) or NHR″ (with ultimate transpeptidation), and that, in order to effect such activation, the enzyme combines with the oxygen atom of the carbonyl group,* thus leading to an electronic deformation analogous to that postulated for the acid-base catalysis of amides and esters.[13]

Earlier work on the specificity of the protein-splitting enzymes has demonstrated that each enzyme hydrolyzes only such peptide bonds as are present in a particular structural setting.[4, 10] Thus, the only peptide bonds known to be hydrolyzed by crystalline trypsin involve the carbonyl group of an arginine or lysine residue, and, in addition, the amino group of the basic amino acid must be suitably acylated. In general, it may be said that a proteinase, in acting on one of its substrates, must combine not only with the oxygen atom at the sensitive peptide bond, but also with another portion of the peptide "backbone"[10] such as the imino group of the adjacent amide linkage and, in addition, with a characteristic side chain group which differentiates the α-amino acids from one another. It is only through a precisely defined "polyaffinity" relationship of this kind that it is possible to explain adequately the striking stereochemical specificity of the proteolytic enzymes.[10] In the case of the enzymatic components of papain that act on benzoylglycinamide and on carbobenzoxy-L-methioninamide, the structural relationship of enzyme to substrate may be formulated as is shown in Fig. 1. Since the action of the enzyme involves the activation of the carbonyl group, the same structural factors in the substrate determine the rate of hydrolysis and the rate of transpeptidation. It follows, therefore, that the

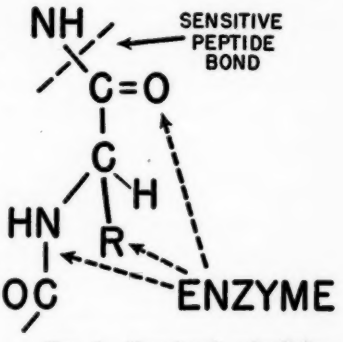
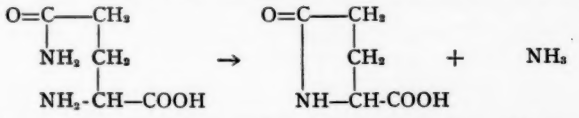


FIG. 1. Postulated polyaffinity relationship between a proteinase and its substrate, leading to enzyme-catalyzed hydrolysis or transpeptidation.

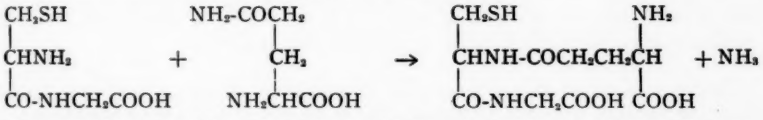
* Additional evidence in favor of the hypothesis that the action of a proteinase on its substrate involves the oxygen atom of the peptide carbonyl group is provided by the important finding of Neurath and his associates[14] that proteinases such as trypsin hydrolyze ester linkages, *i.e.*, linkages in which the —NHR group attached to the peptide carbonyl group has been replaced by an —OR group.

same precise specificity already shown for the hydrolytic action of the proteolytic enzymes applies to their catalysis of replacement reactions.

It is a reasonable assumption that, *in vivo,* enzymes that catalyze hydrolytic or synthetic reactions involving peptide bonds also catalyze transpeptidation reactions. As pointed out by Bergmann,[9] proteolytic enzymes encounter a variety of amino acid derivatives and peptides in living systems, and the probability of such replacement reactions is appreciable. To illustrate the nature of transpeptidation reactions that might be expected in biological systems, one may consider the example of the γ-amide of L-glutamic acid, L-glutamine, which is widely distributed in plant and animal tissues.[1] It is well known that, *in vitro,* glutamine readily undergoes a transamidation reaction leading to pyrrolidone carboxylic acid:



The suggestion may be made that, under the influence of specific enzymes, of which glutaminase may be a representative, the amide group of glutamine may undergo a transamidation reaction, not with its own α-amino group, but with the amino group of another amino acid or peptide. If this were the case in the reaction with the dipeptide L-cysteinylglycine, there would result the naturally occurring peptide glutathione:



This reaction provides an example of the synthesis of a tripeptide from a dipeptide and an amino acid amide, and in which the driving force for the synthetic process is provided by the energy of the amide bond. Experiments performed by Dr. Sofia Simmonds in this laboratory some years ago, using radio-sulfur as a tracer, provided suggestive, but not conclusive, evidence for the reaction between cysteinylglycine and glutamine in rat liver slices. More definite experimental data on this question are sorely needed.

It may be noted that Speck[18] has shown that the biosynthesis of the γ-amide bond of glutamine probably involves the formation of a phosphorylated intermediate, whose formation is in turn coupled to oxidative processes. If this be the case, the *in vivo* synthesis of glutathione may well

represent an instance in which an energy-yielding oxidative step is coupled, through glutamine, to the energy-requiring synthetic step in the process of peptide synthesis. The recent data of Bloch,[6] which have shown that adenosine triphosphate is necessary for the incorporation of isotopic glutamic acid into glutathione by liver extracts and homogenates, would be compatible with the hypothesis presented above.

A logical extension of these views to the problem of the biosynthesis of the peptide bonds of proteins would be to assume that proteolytic enzymes may catalyze reactions in which peptide chains are lengthened, not by direct condensation reactions with the elimination of water, but by transpeptidations involving the replacement of a short peptide chain (or an amino acid) by a longer one. An attractive feature of this hypothesis is that it would allow the proteolytic enzymes to exert their high selectivity of action in reactions in which the free energy change would be small. In the last analysis, of course, the energy required for the synthesis of peptide bonds must stem from exergonic reactions such as those involved in the dissimilation of metabolites; the question may be raised, however, whether the necessary coupling between the energy-yielding processes and peptide synthesis is funnelled through a relatively small number of amides or peptides such as glutamine or glutathione. The utilization, by transpeptidation, of the energy available for protein synthesis would require catalysts of extreme specificity which could direct, precisely and reproducibly, the sequence of chemical reactions leading to the formation of a protein. To our knowledge, the proteolytic enzymes are the only available biocatalysts that act as peptide bonds with this requisite specificity.

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STUDIES IN VASCULAR REPAIR

IV. The Use of Free Vascular Transplants for Bridging Arterial Defects. An Historical Review with Particular Reference to Histological Observations*

GERD SCHLOSS AND HARRIS B. SHUMACKER, JR.

At the close of the last century, during the same period in which the first important steps were being made towards the development of safe and reliable methods for lateral suture and end-to-end anastomosis of arteries and veins, the first efforts were being directed to the possible use of free vascular transplants for bridging defects of arteries. A high degree of success was obtained in the experiments of Carrel and his associates during the early years of the present century—experiments which were hailed with enthusiasm and repeated by investigators in a number of countries. A few instances of successful clinical use of free vein transplants in the surgery of aneurysms were also reported. The hoped-for success of this method was not, however, realized when it was put to clinical trial during World War I. Thrombosis and infection were two factors which vitiated efforts to save extremities with damaged arteries by blood vessel transplantation. Once again ligation became the method of choice. Undoubtedly, in part at least, it was because of these disappointing results that little work in this field was carried out in the years between the two world wars.

Interest in the use of vascular grafts arose anew during World War II. Again large numbers of patients with traumatic division of important arteries served as an urgent incentive for the development of some method which would permit restoration of the continuity of the artery. New chemotherapeutic agents and antibiotics were available and offered promise of less difficulty from wound infections. Anticoagulants were also available and had been demonstrated to be effective in reducing the hazard of thrombosis. Again, however, few successes were achieved in the acutely wounded. The exigencies of warfare, the inevitable delay before battle casualties could be given definitive surgical treatment, the relatively few medical officers with experience in the techniques of vascular repair, and

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the common widespread character of the injuries which obviated sufficiently secure hemostasis to permit the use of anticoagulants were all important factors. Nevertheless, the obvious desirability of restoring blood flow through the damaged artery in these cases and the successes obtained with the maintenance or restoration of the continuity of the affected artery in the elective surgery of aneurysms and arteriovenous fistulas did much to arouse interest in the general problem of vascular repair and in the use of free transplants for bridging arterial defects. This interest has been further increased by the recent extension of the scope of vascular surgery in the field of congenital malformations of the heart and great vessels.

As a concomitant of our own investigations into the function and ultimate fate of vascular transplants[58] we have thought it wise to review the literature in order to bring the past experiences with such grafts up to date. Our attention will be directed primarily to the histological alterations which have been observed in the transplants. It should be mentioned in passing, however, that the actual technique of anastomosis has been of the same concern in the interposition of vascular grafts as it has been in the problem of direct suture of divided vessels. Almost every conceivable method has been tried to facilitate vascular suture, or to substitute a non-suture method, or to bridge gaps in arteries by the insertion of inert tubes. De Gaetano[22] used a removable glass splint during suture anastomosis. In recent years Smith[59, 60] has reported the facilitation of vascular suture by the use of soluble dextrose rods within the lumen. In general, however, no intraluminal splints have been found necessary for successful suture either in direct anastomosis or in the interposition of grafts. The use of stay sutures to triangulate[9, 17] or quadrangulate[25] the opposed ends of the vessel has proved generally adequate.

A number of methods have been proposed for uniting vascular structures without sutures. Payr[37] used absorbable magnesium rings. They were modified by Lespinasse, Fisher, and Eisenstaedt.[45] Recently a similar non-suture technique utilizing vitallium tubes has been advocated by Blakemore, and his associates.[2, 3, 4, 5] Swenson and Gross[62] have employed absorbable fibrin tubes with success. There can be no doubt that these methods are contributions of value and they will certainly have a place in vascular repair in certain situations where suture techniques are impossible or can not be carried out properly. That suture techniques are preferable, however, is indicated by the experiments of Murray and Jones[52] and Johns,[48] and most vascular surgeons prefer suture methods except in the most unusual circumstances.

Abbe[1] had tried without success the use of glass tubes as a permanent intraluminal prosthesis. Whenever glass tubes have been used to bridge gaps in blood vessels, thrombosis has invariably occurred. Recently, to be sure, more promising results have been reported with lucite[40] and polyethylene tubes.[24] At the present time, however, it seems fair to say that it is unlikely that any inert tubing will prove as satisfactory as properly utilized vascular transplants for permanently bridging gaps in arteries.

It should also be mentioned that there has been general agreement since the experiments of Murray[50, 51] that the use of anticoagulants enhances the chance of success of any vascular repair.

In reviewing the literature concerning the histological fate of vascular transplants it is apparent that, except for work currently being carried out, this aspect of the problem has received little or no consideration in recent decades. Unfortunately too, most of the work recently completed has not yet been published. A great deal of valuable information is to be found in the older literature. Nevertheless it must be recognized that some of the early descriptions are incomplete and lack clarity. Moreover, most authors dealing with this phase of the problem have had at their disposal few successful grafts of more than the briefest duration. We have excluded from consideration remarks concerning the histological appearance of grafts which were occluded by an obturating thrombus since pressure of the circulating blood upon the wall of the graft is an important factor in the histogenesis of structural changes in its wall. We have, however, included cases in which small flat mural thrombi were present without impairing blood flow through the transplant.

Fresh autografts

Arterial autographs. The first vascular transplants were the arterial autografts of Clementi[20] and Jaboulay and Briau,[42] but thrombosis occurred in all of them as well as in the experiments of Exner.[25] Höpfner[28] was the first to perform a successful arterial autograft. Sixteen histologically studied cases of arterial autografts were found in the literature. All of them had been performed in dogs.

Borst and Enderlen[7] reported three observations. One was a carotid reimplantation of 122 days' duration; one a contralateral carotid transplantation of 10 days' duration; another a contralateral carotid transplantation of 14 days' duration. The grafts were described as unchanged except for a thickening of the intima by a growth of young connective tissue which extended from the suture lines; the thickened area contained delicate newly

formed elastic fibers. Stich and Zoeppritz[61] described the same intimal thickening in a femoral transplant to a carotid defect 14 days old; they thought this process arose in the graft itself. Yamanoüchi[70] made essentially the same observations as Borst and Enderlen, a thickening of the intima with newly formed elastic fibers extending on the transplant from the suture lines. His studies were based upon examination of four transplants varying in age from 7 to 108 days. The youngest was a reimplantation of the abdominal aorta, the oldest a carotid reimplantation. Two carotid transplants to a femoral defect were 86 and 95 days in age. Castiglioni[18, 19] in studying five grafts, carotid reimplantations, or contralateral transplantations varying in age from 63 to 250 days, also noted no alteration except intimal thickening with newly formed elastic fibers near the suture lines. In a 250-day-old graft this thickening, though slight, was found throughout the graft.

In contrast, a few observers described the transplants as entirely normal. Such was the case with the 28-day-old contralateral carotid graft of Guthrie and his associates,[35, 36, 44] with the 93-day-old carotid reimplantation of Villard and his co-workers,[65, 66, 67] and with the 91-day-old femoral artery graft to a carotid defect recorded by Moure.[49]

In summary it may be said that the wall of the fresh arterial autograph upon examination from 10 to 250 days after operation is described as undergoing no change or only intimal thickening. The graft would appear to survive as a living structure.

Venous autografts. The earliest experiments with venous autografts were those of Gluck,[29] Exner,[25] and Höpfner[38]; all resulted in failure. Carrel and Guthrie[14, 15, 16] were the first to succeed; they transplanted in dogs the external jugular vein to the carotid artery and the femoral vein to the femoral artery. At the same time Goyanes[31, 32] performed 15 transplants of inferior vena cava to the abdominal aorta of dogs, but all save one ended in failure, the exceptional case showing grossly only a fibrinous layer over the suture lines when examined on the thirteenth day. Altogether 40 cases of venous autografts examined histologically were found in the literature. They were all performed on dogs unless otherwise indicated.

Carrel and Guthrie[15, 16] described intimal thickening and an increase in connective tissue in the media and adventitia in a 14-day graft of jugular vein to carotid artery. Subsequently Carrel[12] reported studies in three cases—two instances of transplantation of vena cava to abdominal aorta in the cat, 32 and 303 days in age, and one 415-day-old similar transplant in a dog. In 32 days he found the media was composed chiefly of connective

tissue. Elastic fibers were absent in this specimen and were seen infrequently in the 303-day-old graft, the media of which was entirely composed of connective tissue. In the specimen 415 days old, however, the muscle cells seemed to be increased in number in addition to the increase in fibrous tissue in the media. In this case there was also a little intimal thickening. The adventitia was considerably thickened by fibrous tissue in all three cases. Carrel supposed that a vein graft could undergo functional hypertrophy (increase in muscle and connective tissue) with a tendency towards arterialization, or could undergo progressive sclerosis with disappearance of the muscle cells; he further supposed that the sclerosis might develop as an aftermath of the hypertrophy. He found some evidence for this assumption in another case[10, 12] in which a small piece of a jugular vein transplant into a carotid defect was extirpated in 143 days and showed a sclerosed media containing an increased number of muscle cells, while in 605 days the remaining graft showed further sclerosis with disappearance of all the muscle. Watts[69] found an increase in the subendothelial tissue resulting in intimal thickening, as well as fibrous thickening of media, adventitia, and periadventitia in a 26-day-old transplant to the carotid artery.

On studying seven cases of jugular transplants to the carotid artery ranging in age from 19 to 86 days, Fischer and Schmieden[27] found the intima for the most part unchanged. In some instances, however, there were between the endothelium and media large flat thickenings composed of a dense layer of long spindle-shaped cells which appeared to be connective tissue cells but which at times had a striking resemblance to smooth muscle cells. These thickened areas were only found near the suture lines and were almost entirely free of elastic fibers. The authors assumed an inflammatory histogenesis, an endothelial proliferation provoked by minute lesions of the intimal surface during operation. Against the assumption that these thickenings were of a compensatory nature due to the high blood pressure the authors stated (i) that these thickenings were found relatively early and did not increase in thickness later, (ii) that they were not found in places remote from the suture lines, and (iii) that they did not occur in other experiments in which jugular veins were subjected to arterial pressure by anastomosis with the carotid artery. In addition to the intimal changes described, the media of the transplants showed hypertrophy and hyperplasia of the muscle cells and an increase in connective tissue. It could not be determined whether the diminution in elastic fibers was the result of stretching of the vessel wall or represented a real reduction in number. The

adventitial connective tissue was described as tighter and firmer than normal.

Stich and Zoeppritz[81] studied three cases of jugular grafts to the carotid artery, 26, 211, and 409 days in age. In all three they found a considerable thickening of the intima with new formation of elastic fibers. In the 211-day specimen this thickening was irregular and wave-like. In the 409-day specimen the intima in the mid-portion of the graft was composed of a single layer of cells whereas there was considerable thickening nearer the suture lines. The media and adventitia were described as unchanged in all three instances except for a stretching of the elastic fibers. The authors assumed that the thickening of the intima was the result of the arterial pressure and that the new cells arose from the venous endothelium.

Borst and Enderlen[7] described the same intimal thickening in a 19-day-old jugular transplant to the carotid artery. This thickened intima showed newly formed elastic fibers and it decreased in thickness towards the middle of the graft. There were smooth muscle cells in the thickened areas. Since these changes were observed at a distance from the suture lines, the authors assumed that they resulted from the arterial blood pressure. The media showed hypertrophy and hyperplasia of muscle cells, there was a marked increase in the connective tissue of media, adventitia, and periadventitia, and the elastic fibers appeared to be stretched far apart.

Guthrie and his associates[35, 36, 44] described complete absence of muscle cells and a very pronounced adventitial fibrosis in a 28-day-old transplant of jugular vein to carotid artery. In studying one 85-day-old graft of femoral vein to femoral artery and three grafts of jugular vein to carotid artery 51, 66, and 297 days in age, Yamanoüchi[79] described intimal thickening of the entire graft with newly formed elastic fibers, moderate increase in the number of muscle cells, and marked connective tissue proliferation in the media and adventitia. He, too, assumed that the intimal thickening was produced by the blood pressure. Curcio[21] examined a 23-day-old jugular transplant to the carotid artery and found fibrous thickening of the intima with delicate elastic fibers which decreased in number towards the mid-part of the graft. Palazzo[55, 56] reported no changes in a 10-day-old jugular graft to the carotid artery. In similar specimens studied 50, 100, 475, and 483 days after transplantation, however, he described a newly formed subendothelial layer of connective tissue without smooth muscle cells or elastic fibers, as well as hypertrophy and hyperplasia of the muscle cells of the media and an associated increase in collagenous and elastic tissue. Villard and his associates,[65, 67] on examining a similar jugular trans-

plant 113 days old, described the same thick subendothelial layer of connective tissue. Although they found no elastic fibers they did find smooth muscle cells, the presence of which led them to assume that arterialization of the venous graft had taken place. They noted no changes in the media; the adventitia was thickened by fibrous tissue. Castiglioni[18, 19] examined two jugular transplants to carotid arteries 20 and 37 days old and a 195-day-old graft of femoral vein to carotid artery. He described a thickening of the intima from proliferation of endothelial cells and new elastic fibers and he, too, assumed these changes to be of a compensatory character. Hyperplasia of the medial and adventitial connective tissue as well as hypertrophy of the medial muscle cells were noted.

Moure[49] studied six similar jugular grafts varying in age from 23 to 137 days. He found a subendothelial layer of spindle-shaped cells, which he considered to be smooth muscle cells, and newly formed elastic fibers. Again hypertrophy of the muscle cells and elastic fibers of the media was noted as well as fibrous thickening of the adventitia. In an additional case Moure[48, 49] excised a segment, one cm. in length, from the mid-portion of an 801-day-old jugular graft and in its place inserted a segment from the normal contralateral jugular vein. Histological description of the excised specimen was limited to the remark that there was hypertrophy of the wall and formation of a subendothelial layer. Thirty-seven days later the dog was sacrificed, and the second venous graft was said to have been as thick as the original graft. The author considered that the experiment gave evidence that the venous autograft persists as a living structure since it is capable of receiving and gaining firm union with a second graft. No histological study was reported.

Goodman's[30] 8-day-old femoral vein transplant to a carotid artery was said to have shown degeneration of the wall.

In summary it may be said that histological examination of specimens ranging in age from 8 to 801 days led all investigators to the general conclusion that venous autografts persist as living structures but undergo certain histological changes consisting chiefly of fibrous reinforcement. It was generally supposed that these alterations resulted from the arterial pressure exerted upon the transplant. There was considerable difference of opinion concerning the nature and degree of the structural changes.

Fresh homografts

Arterial homografts. Höpfner[36] was the first to perform a successful arterial homograft; he transplanted the femoral artery of a dog to the

carotid artery of another dog. We have found in the literature histological studies of 22 arterial homografts ranging in age up to a maximum of 3 months. Unless otherwise indicated, all were transplants from one dog to another.

Ward[68] examined an aortal graft to another aorta 70 days after operation. He found the muscular and connective tissue layers well preserved; there was a very slight decrease in the amount of elastic tissue. Borst and Enderlen[7] studied two specimens, one a 22-day-old carotid transplant to the carotid artery of a second dog, the other a 29-day-old carotid artery transplant to the carotid artery of a second goat. In both they found signs of destruction of the graft—lack of nuclear staining, break-down of elastic fibers, swollen adventitial collagenous tissue, and infiltration of the wall with polymorphonuclear leucocytes. There was a layer of young connective tissue on the external surface of the adventitia. Flat mural thrombi were seen on the intima in the specimen from the dog. The whole intimal surface of the goat transplant was covered with a thin layer of connective tissue containing smooth muscle cells and elastic fibers. The same tissue filled the suture lines. The authors assumed that the fibroblasts in this tissue were derived from the endothelium of the carotid of the host and that the smooth muscle cells had, in turn, been derived from these fibroblasts.

Stich and Zoeppritz[61] found no changes in three carotid transplants to other carotid arteries when examined 4, 5, and 11 days after operation. Yamanoüchi[70] also found a 10-day-old aorta to carotid graft normal in appearance. Only a thickening of the intima with newly formed elastic fibers was noted extending for some distance from the suture lines. In a similar graft 36 days old, however, the nuclei in the media did not stain, the elastic fibers were fragmented, and the adventitia contained polymorphonuclear leucocytes and fibroblasts extending towards the media. The internal surface of the graft was covered by a thickened intima which contained elastic fibers. Two additional grafts of carotid artery to carotid artery, 27 and 74 days in age, showed the same alterations with the exception that the intimal thickening was confined to the ends of the transplants.

Villard and his associates[63, 65, 67] studied two cases, one an 11-day-old graft of iliac artery to carotid, the other a 62-day-old carotid to carotid transplant. Again in the early specimen no alterations were noted. In the older specimen, however, the muscle cells had disappeared though the elastic fibers were still visible. The internal surface was covered by a layer of young connective tissue and smooth muscle cells and there was newly formed connective tissue in the adventitia. Similar observations were made

by Ingebrigtsen[41] who examined eight specimens 3 months in age, all carotid to carotid transplants in cats. The muscle cells were either normal, degenerating, or absent, the elastic fibers were normal, there was a fibroblastic thickening of the intima, and in some there was increased connective tissue in the adventitia. In a 63-day-old carotid to carotid graft Castiglioni[18, 19] noted almost complete absence of muscle cells, breaking down of elastic fibers and some intimal thickening. Goodman[30] described a 21-day-old carotid to carotid transplant as undergoing destruction with the elastic tissue in the process of fragmentation. An increase in connective tissue was noted on the outer surface of the adventitia.

In summary it may be stated that the majority of authors seemed agreed that after a brief interval the arterial homograft exhibited signs of destruction and of reinforcement by connective tissue proliferation from the outside.

Venous homografts. Only one histological description of a venous homograft was found in the literature. Yamanoüchi[70] described a jugular transplant to a carotid artery 119 days in age. The wall was replaced by dense connective tissue. Muscle cells and elastic fibers were absent. The entire internal surface was covered by a thickening of the intima; newly formed elastic fibers were contained in this layer.

Fresh heterografts

Arterial heterografts. The initial efforts with arterial heterografts made by Höpfner[35] resulted in failure. Carrel[9] and Guthrie[33] were the first to achieve success with heterografts; Carrel's early investigations were with preserved arteries. Ten instances of histological examination of fresh arterial heterografts were found in the literature.

Ward[68] examined a 20-day-old transplant of cat aorta to the carotid artery of a dog. He found very slight loss of elastic tissue, a beginning breaking down of muscle fibers, and proliferation of new connective tissue. In a 70-day-old transplant of rabbit aorta to the carotid of a dog the intima was found replaced by a layer of hyalinized fibrin and blood. The muscle cells had disappeared almost entirely and the elastic fibers had disappeared completely. Newly formed connective tissue had replaced the original vessel wall to a considerable extent.

Stich and Zoeppritz[61] examined two grafts of cat aorta to the carotid artery of dogs. In one, 15 days old, the intima and the inner layers of the graft were well preserved. Externally the graft was surrounded by fresh scar tissue which was growing into the graft. In the other, which was 52

days old, only scanty rests of media showing degeneration of elastic fibers were seen. The adventitia was replaced by scar tissue. A thick layer of vascular granulation tissue was found growing from the suture lines into a flat mural thrombus which covered the whole inner surface of the graft. A third transplant, a 51-day-old graft of rabbit aorta to the carotid of a dog, also showed only scanty remnants of media infiltrated by granulation tissue. The internal surface of the graft was covered by flat mural thrombi and a thick fibrous layer containing newly formed elastic fibers. Scar tissue had replaced the adventitia. In another case, a 14-day-old transplant of human posterior tibial artery to the carotid of a dog, granulation tissue was found growing into the adventitia and outer layer of the media. The inner layer of the media was normal in appearance and endothelium appeared to be growing from the suture lines over the internal surface of the graft.

In a 214-day-old transplant of rabbit aorta to the carotid of a dog Guthrie and his associates[35, 36, 44] found the muscle cells and elastic fibers had disappeared and been replaced by dense, partly hyalinized connective tissue with some calcification and osteogenesis. There was a layer of living connective tissue between the endothelium and the transplant, and another layer of connective tissue covered the external surface of the graft.

Yamanoüchi[70] found the media somewhat necrotic in a 12-day-old transplant of dog iliac artery to the aorta of a cat. There was an intimal proliferation with newly formed elastic fibers extending over the graft from the suture lines. In a 42-day-old specimen of cat aorta transplanted into a carotid defect in a dog the media was amorphous, the elastic fibers fragmented, and, as in the other case, intimal proliferation. Both specimens showed growth of connective tissue on the external surface of the graft.

A 35-day-old transplant of rabbit aorta to the carotid of a dog was described by Villard and his associates[23, 64, 65, 67] as showing some intimal thickening near the suture lines with the mid-portion of the inner surface of the graft covered with fibrin. There were islands of fragmented elastic fibers in the media and inflammatory infiltration in the adventitia.

No histological study of fresh venous heterografts was found.

In summary it may be concluded that after a short interval fresh arterial heterografts show evidence of destruction and of reinforcement by connective tissue proliferation.

Preserved vascular transplants

Preserved arterial homografts. Carrel[11] was the first to investigate the functional and histological results with preserved arterial homografts. In

an extensive study he used as grafts carotid arteries of dogs kept in a refrigerator in different media for varying periods of time. The media used were physiological saline solution, Locke's solution, humid air, vaseline, serum, and defibrinated dogs' blood. Carrel arrived at the conclusion that these blood vessels were in a condition of "latent life," based upon the observation that after transplantation there occurred only partial or no degeneration of their walls and the muscle cells maintained their normal appearance for a long time after operation, while rapid degeneration of the wall occurred after transplantation of "dead" blood vessels. According to the histological descriptions, however, there can be no doubt that these grafts preserved in "latent life" underwent the same degenerative changes observed in fresh arterial homografts. When examined shortly after transplantation the elastic fibers were found unchanged and the muscle cells only partially destroyed. After longer periods of observation, the longest being 660 days, the elastic fibers were in large part well preserved but the muscle cells were replaced by connective tissue. In some cases the intima was thickened by connective tissue composed of elongated cells, the nuclei of which resembled muscle cell nuclei, and by newly formed elastic fibers. The thickened intima was covered by endothelium. The adventitia was thickened by connective tissue proliferation.

In reviewing these studies it is impossible to decide which of these preserved vessels were still in a condition of "latent life" at the time of transplantation and which were completely dead. The criteria which Carrel used would seem applicable only to autografts in which survival or death of tissue after transplantation would be the basis for judging whether the graft was alive at the time of transplantation or not. The histological results might be similar in living or dead homografts. If the tissues were viable they would probably also possess their serological properties and would be destroyed by the host. If already dead, the result might be the same. It would appear that the questions he attempted to answer—the length of time vessels could be kept in "latent life" and the best medium for storage—were not answered.

Carrel also carried out three experiments with homografts preserved by drying over calcium chloride and placed in Locke's solution immediately before transplantation. One graft was successful and was examined after 202 days. The muscle cells had disappeared, the elastic fibers were normal, the adventitia somewhat thickened, and the intima was thickened by connective tissue cells and thin elastic fibers. In two other experiments homografts were left at —3° C. for several days. Both were thrombosed

when examined after 5 and 85 days respectively. Bode and Fabian[9] repeated Carrel's experiment, but thrombosis occurred in most of the grafts and the age of the graft was only a few days in the successful experiments.

Yamanoüchi[70] used as transplants to carotid or femoral arteries specimens of aorta kept for from 3 to 9 days in Locke's solution in a refrigerator. The grafts were 9, 24, 103, and 143 days old at the time of study. The same observations were noted as in fresh homografts—intimal thickening with newly formed elastic fibers, disappearance of muscle cells, fragmentation and reduction in number of elastic fibers, ingrowth of granulation tissue from the outside into adventitia and media. The two oldest specimens also showed calcification. In another 24-day-old graft to carotid artery of a segment of aorta, kept refrigerated for 5 days in physiological saline solution, the muscle cells and elastic fibers were well preserved; there was a growth of granulation tissue extending into the adventitia and media. In two other experiments Yamanoüchi used for grafts to the abdominal aorta transplants kept for 5 and 10 days respectively in sterile water in a refrigerator. One was examined 8 days after operation. The muscle cells stained poorly or not at all, the elastic fibers were fragmented and irregularly stained, and granulation tissue was seen growing into the adventitia from the surrounding tissues. The other specimen was studied 81 days after transplantation. The muscle cells were necrotic, the elastic fibers degenerated and reduced in number, the periadventitia and adventitia occupied by dense connective tissue which also was observed to be growing into the outer portion of the media. There was intimal thickening over the entire graft.

Villard and his associates[63, 65] examined one 48-day-old transplant of a carotid artery kept for 19 days in a refrigerator before being used as a graft to a carotid artery. An entirely newly formed intima was found. Again the muscle cells had disappeared. The elastic fibers were still visible. The adventitial area was occupied by newly formed connective tissue, the fibroblasts of which were growing into the media. The original graft was described as interposed like a "sequester" between newly formed intima and adventitia. In another experiment Villard and his associates[65, 67] also studied a 34-day-old graft of an iliac artery kept for 67 days in artificial serum in a refrigerator before transplantation to a carotid. The more resistant parts of the elastic framework of the graft were preserved, while the rest had undergone atrophy and resorption. No newly formed intima could be seen.

In summary it would appear that preserved arterial homografts

behave much like fresh homografts, undergoing degeneration and fibrous replacement.

Preserved venous homografts. Only one specimen studied histologically was found in the literature. In this case Carrel[13] kept a jugular vein in cold storage for 24 hours before transplanting it to the thoracic aorta. When examined 802 days later, neither muscle cells nor elastic fibers were found preserved. Endothelial cells were seen on the internal surface of the graft.

Preserved arterial heterografts. Carrel[9] had two successful results in four arterial heterografts preserved in the refrigerator for from 3 to 20 days in physiological saline solution, defibrinated blood, or Locke's solution. No histological examination was carried out. Subsequently[13] he transplanted a human popliteal artery to a dog's abdominal aorta after keeping it for 24 days in a refrigerator in physiological saline solution. The specimen was examined 4 years and 2 months later. No muscle cells or elastic fibers were seen, the vessel consisting exclusively of connective tissue with areas of hyaline degeneration.

Moure[40] transplanted a human popliteal artery to a dog's carotid after keeping it for 24 hours in physiological salt solution in a refrigerator and for another 48 hours in vaseline at room temperature. The graft was studied 53 days after operation. Muscle cells were absent. The graft was composed of a fibrous-elastic scaffold embedded in fibrin.

Preserved venous heterografts. Carrel[9] made the first attempt to transplant a preserved venous heterograft. After keeping a segment of jugular vein from a dog in physiological saline solution in a refrigerator for 7 days he sutured it into an aortic defect in a cat. When examined 22 days later, the segment was occluded by a thrombus. Only two histological studies of preserved venous heterografts were found in the literature.

Bode and Fabian[8] kept a human saphenous vein in a refrigerator for 2 days and then transplanted it to a dog's brachial artery. Upon examination 130 days later, a spindle-shaped dilatation of the graft with marked thickening of its wall was noted. No muscle cells and only remnants of elastic fibers were seen. The wall of the graft was replaced by connective tissue, partly hyaline in appearance. Villard and his coworkers[65, 67] kept a human popliteal vein in artificial serum in a refrigerator for 24 hours before suturing it into a defect of a dog's abdominal aorta. Twenty days later an aneurysm was found in the region of the graft. The original vein was almost entirely degenerated and only the elastic fibers were visible.

In summary, the preserved arterial and venous heterografts underwent degeneration with replacement of connective tissue from the host.

Fixed vascular transplants

Arterial transplants. Guthrie[33] was the first to transplant successfully a formalin-fixed arterial graft. In this instance a segment of cat aorta was transplanted to the carotid artery of a dog. We have found in the literature six histologically studied cases of successful transplantation of fixed arterial grafts. They ranged in age from 6 days to 3 months; all were homografts in dogs.

Levin and Larkin[46, 47] studied 3 grafts of formalin-fixed thoracic aorta used as transplants to abdominal aorta, 9 and 11 days and 10 weeks after operation. In the earliest specimen the inner half of the graft was entirely necrotic and the outer half appeared to be undergoing degeneration. The elastic fibers were preserved. In the 11-day-old graft the entire wall was homogeneous; elastic fibers were stained but seemed swollen and diminished in number. In the oldest specimen the wall of the graft showed zones of calcified material interlaced with badly damaged and swollen elastic fibers. There were occluding thrombi at both ends of the graft. In all three specimens the external surface of the transplant was covered with a sheath of connective tissue.

Bode and Fabian[6] found normal staining quality of nuclei and elastic fibers in a 6-day-old transplant to femoral artery of a formalin-fixed segment of carotid artery. Yamanoüchi[70] found no nuclear stain in the media and fragmentation and reduction in number of elastic fibers as well as thickening of the intima containing elastic fibers. His specimen was a 24-day-old graft of formalin-fixed aorta transplanted to a carotid artery.

Nageotte and Sencert[53, 54] studied a 3-month-old alcohol-fixed carotid graft transplanted to another carotid. The inner surface was said to be covered by a new intima formed by proliferation and overgrowth of the endothelium of the artery of the host. Underneath the new intima, near the suture lines, there was a layer of smooth muscle cells thought to be derived from the media of the host artery; these cells were called "myome de régénération." The muscle cells of the media of the graft had disappeared but immigrated fibroblasts, transitional cells from fibroblasts to muscle cells and smooth muscle cells were visible. The elastic fibers were preserved. Adventitia and periadventitia had a relatively normal appearance due to immigration of fibroblasts which replaced the original connective tissue cells; the original collagenous fibers remained unchanged. This process was termed connective tissue "reviviscence."

Several later workers had less success. Fici and Speciale[28] found all six of their formalin-fixed grafts thrombosed when studied from 3 days to 3

months after transplantation. Hosomi[39] found the lumen obliterated in 21 alcohol-fixed grafts examined from 8 to 407 days after operation.

Venous transplants. Only one histological study of a previously fixed venous graft was found in the literature. This specimen studied by Guthrie and his associates[24, 26, 27, 44] is, however, of remarkable interest since it was examined 11 years and 2 months after transplantation. A segment of vena cava of a dog was fixed in 2.5 per cent formalin for 60 days, washed in dilute ammonia, dehydrated in absolute alcohol, and impregnated with paraffin oil before transplantation to the carotid of another dog. The animal died over 11 years later of a metastasizing sarcoma of the sternum. At the site of the graft a spindle-shaped aneurysmal dilatation was seen. A small strip of the original graft was still recognizable histologically; it consisted of hyaline connective tissue with some granules representing remnants of elastic fibers. The original transplant was surrounded on intimal and external surfaces by a sheath of connective tissue; endothelium covered the intimal surface. There was calcification in the remainder of the graft and in the subendothelial layer of connective tissue.

In summary it would appear from the few observations reported that dead fixed arterial and venous transplants may result in functional success. The graft tends, like fresh and preserved homo and heterografts, to be replaced by connective tissue.

Discussion and summary

In spite of certain limitations and points of disagreement the early studies of vascular transplants have given us valuable information concerning the histological fate of these grafts. There seems to be general agreement that fresh arterial autografts survive as living structures with either no change or only intimal thickening. There is also general agreement that fresh venous autografts likewise survive as living transplants but undergo more marked histological changes consisting chiefly of fibrous reinforcement. Most investigators assumed that these changes were the result of the arterial pressure upon the graft. Considerable difference of opinion was expressed concerning the nature and degree of the structural changes, especially as to whether the smooth muscle cells of the media remain unchanged, or undergo hypertrophy and hyperplasia, or disappear after a short interval. These differences may be explained, in part at least, by the variation in the histological appearance of the normal vein, not only in different regions of the body, but also in the same region of different individuals of the same species, and even in the course of the same vein.

After a brief interval most of the fresh arterial homografts were found to show signs of destruction and of reinforcement by connective tissue proliferation from the host; the same was true of the one fresh venous homograft studied. Fresh arterial heterografts similarly seemed to undergo destruction with fibrous replacement. No histological study of fresh venous heterografts was found in the literature. In general, arterial and venous homografts and heterografts preserved in a cool atmosphere in various media before transplantation similarly showed evidence of degeneration and fibrous replacement. Previously fixed vascular transplants showed fibrous reinforcement and varying degrees of disintegration.

A question of considerable interest concerns the structure and histogenesis of the intimal thickening of the transplants the cells of which have been described by several investigators as smooth muscle cells derived from fibroblasts. Since the transformation of fibroblasts into smooth muscle cells in postembryonic life is a much-debated problem, a clear-cut definition of these cells would be valuable. This point will be discussed further in connection with our own studies of venous transplants.[58]

It appeared evident from our review that, in spite of marked differences in histological fate, all types of vascular transplants were capable of functionally bridging arterial defects.

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NEWS AND COMMENT

The Association of Yale Alumni in Medicine is planning an active program. The Executive Committee met on Nov. 18 and on Jan. 8 at the home of the Chairman, Dr. Clyde Deming. Plans for a program on Alumni Day, February 22, were made. The Committee also considered how it might help and be helped by the YALE JOURNAL OF BIOLOGY AND MEDICINE, and how it might assist the School significantly to nourish and improve its teaching program. The results of its deliberations when they have been further clarified will be submitted to the members of the Association. Dr. Elihu Wing, Ph.D. 1911, M.D. 1915 of Providence, Rhode Island, is President. Vice-presidents are Vernon S. Lippard, B.S. 1926, M.D. 1929; J. Roswell Gallagher, B.A. 1925, M.D. 1930; Samuel D. Kushlan, B.S. 1932, M.D. 1935; N. William Wawro, M.D. 1938; and William Bevis, M.D. 1940; Marion Leonard Robbins, M.S. 1929, M.D. 1931, is Secretary-Treasurer, and Charles E. Farr, B.A. 1898, M.D. 1903, is a member of the Alumni Board.

Serving Connecticut hospitals. During the current academic year, the School of Medicine, in cooperation with the Hartford Hospital, is conducting formal postgraduate courses or programs in the following Connecticut hospitals: Danbury, Hartford, New Britain, Norwalk, State Hospital for Chronic Disease, Waterbury, and Windham (Willimantic). The Third Postgraduate Seminar in Neurology, Psychiatry, and Related Fields of Medicine, conducted by the School of Medicine, the State Medical Society, and the Joint Committee of State Mental Hospitals, is being held in the following institutions, with the active support of the institutions concerned: the Connecticut State Hospital, the Fairfield State Hospital, the Norwich State Hospital, the U.S. Veterans Administration Hospital at Newington, the Hartford Hospital, the Southbury State Training School, and Yale University.

Recently completed agreements call for the provision of pathology services by the School of Medicine to the Laurel Heights State Tuberculosis Sanitorium, the Griffith Hospital in Derby, and the Lawrence and Memorial Hospitals in New London. The School has been providing such services for the Fairfield State Hospital.

Building plans and progress. Those who have not been to New Haven recently will be interested to know that the block bounded by South, Park, Oak, and York Streets is being cleared of old buildings. The new Unit of the Grace-New Haven Community Hospital is scheduled for construction there beginning sometime in the summer of 1950.

The School of Medicine has plans for a new Cancer Research Laboratory to meet the growing demands of modern research. It will be located as a new wing to the medical center along Congress Avenue to Howard.

Developments in public health. During the last three years the activities of the Department of Public Health, Professor Ira V. Hiscock, Chairman, have been substantially enlarged. Under a short-term grant from the Kellogg Foundation, a two-year course in hospital administration was established under the immediate direction of Dr. Clement C. Clay, Associate Professor of Public Health. This program, now in its third year, has been very successful.

Under a United States Public Health Service teaching grant, a program in cancer control administration has been established. This program, now in its second year under Dr. Edward C. Cohart, Associate Professor of Public Health, is closely coordinated with the Section on Oncology under Dr. S. C. Harvey, and has contributed a valuable teaching service in the field of public health administration. Instruction and research in the administrative aspects of medicine and public health have been strengthened by the addition of Dr. Milton I. Roemer as Assistant Professor through the cooperation of the Public Health Service.

The Institute of Occupational Medicine and Hygiene was assigned to the Department of Public Health last year. Under Dr. J. Wister Meigs, Assistant Professor of Occupational Medicine, and Mr. Robert M. Brown, a chemical engineer trained in public health recently appointed as instructor in occupational medicine, the Institute is developing its teaching and research programs.

The Diagnostic Clinic. A diagnostic clinic was established by the School in 1948 at the request of the Connecticut State Medical Society and with the cooperation of the Society's Committee on Cooperation with the Yale School of Medicine. The purpose of the Clinic is to make available to physicians of the State a complete diagnostic service for referred patients. When requested by the referring physician, surgical and therapeutic service is provided.

Patients are seen on an ambulatory as well as in-patient basis. They receive a complete evaluation by the staff of the Department of Internal Medicine who use such consultants as are required. Members of both the full-time and part-time faculty participate. Only patients referred by a practicing physician are accepted. The clinic staff works in close cooperation with the referring physician. He retains complete control over the disposition of the case, and receives a full report on the diagnostic work-up. Fees are moderate, ranging from a minimum of $25 to a maximum of $150 for ambulatory patients.

Dr. Hugh L. Dwyer, Jr., is in charge of the Diagnostic Clinic.

Chronic Disease and Rehabilitation Center at the Grace-New Haven Community Hospital and the School of Medicine. In recognition of the importance of this relatively undeveloped field, the Grace-New Haven Community Hospital, with a comparatively small grant from the Connecticut State Commission for the Chronically Ill, Aged, and Infirm, has converted Fitkin II ward into a chronic disease and rehabilitation ward. The

main research effort of the Unit will be devoted to arthritis. As funds become available, it is hoped to enlarge and develop this program, to provide a complete diagnostic, therapeutic, and rehabilitation service, coordinating all the resources of the medical center, and providing new ones as needed in line with modern concepts. This program is affiliated with that of the State Chronic Disease Hospital at Rocky Hill, where a similar program has been in operation for the last two years. These two centers will assist in the training of medical students and house officers in modern concepts and techniques in the care of the chronically ill and in rehabilitation.

Dr. William E. Swift, Jr., Assistant Professor of Medicine, has been placed in charge. A Rehabilitation Study Unit has also been organized consisting of Dr. Swift, Dr. Hilda Kroeger, Assistant Director of the Grace-New Haven Community Hospital, Dr. J. Wister Meigs, Assistant Professor of Occupational Medicine, Dr. Ned M. Shutkin, Instructor in Orthopedic Surgery, Dr. Henry Wexler, Assistant Professor of Psychiatry, and Dr. Nila Kirkpatrick Covalt, Associate Clinical Professor of Medicine.

Faculty changes. Those who have not kept up with faculty changes in recent years may be interested in a few of the more important ones. Dr. Arnold Gesell is now Director Emeritus of the Clinic of Child Development and Professor Emeritus of Child Hygiene. The Clinic of Child Development has been renamed the Child Study Center and is being related closely to the School of Medicine, especially the Departments of Pediatrics and Psychiatry and to all other departments in the University interested in child development. Dr. Milton J. E. Senn has been appointed as Sterling Professor of Pediatrics and Psychiatry in charge of the Child Study Center. Dr. Senn was formerly the Director of the Institute of Child Development at Cornell.

Dr. Milton C. Winternitz, Anthony M. Brady Professor of Pathology and Chairman of the Department of Pathology, and former Dean of the School of Medicine, is now taking a sabbatical leave of absence prior to his retirement on July 1, 1950. His sabbatical year is being devoted to serving as Director of the Childs Fund; as Chairman of the Committee on Growth and Acting Chairman of the Division of Medical Sciences of the National Research Council. Dr. Harry S. N. Greene, Professor of Pathology since 1943, has been named to succeed Dr. Winternitz as Anthony M. Brady Professor of Pathology and Chairman of the Department of Pathology.

Dr. Hugh M. Wilson, Professor of Radiology, resigned July 1, 1949, to accept the position of Director of the Mallinckrodt Institute of Radiology at Washington University, St. Louis. Dr. Arnold H. Janzen, Associate Professor of Radiology, is acting in his place and as Chief Radiologist of the Grace-New Haven Community Hospital.

Dr. Frederick C. Redlich, Associate Professor of Psychiatry, has been serving as Executive Officer of the Department of Psychiatry since 1947

when Dr. Warren Brown resigned to accept the position of Assistant Dean and Professor of Psychiatry at Baylor University.

Faculty honors and activities. Dr. John F. Fulton received the decoration of *Officier* of the *Legion d'Honneur* as announced at the International Neurological Congress, September 5-10, 1949, in Paris. He was also the Ludwig Mond Lecturer at the University of Manchester on October 6, where he spoke on "Humanism in an Age of Science."

Dr. Grover F. Powers received the degree of D.Sc. at Indiana University on the occasion of the laying of the cornerstone for the new research building of the James Whitcomb Riley Hospital for Children.

Dean C. N. H. Long was appointed as one of the Yale representatives on the Board of Trustees of the Brookhaven National Laboratory for a term of three years succeeding Mr. Sinnott.

Doctors Gerald Klatskin, Norton Canfield, and Frederick C. Redlich were consultants to the Surgeon General of the United States Army during the summer and visited various Army installations in Europe.

Dr. Clyde Deming presented a paper to the International Society of Urology, meeting September 20-23 at Barcelona, Spain.

Dr. W. U. Gardner attended the International Cancer Research Commission in Paris during the summer and visited cancer centers in Great Britain.

YALE PUBLICATIONS IN BIOLOGY AND MEDICINE

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BARTON, P. N.: Analysis of fifty cases of back pain. Indust. M., 1949, *18,* 391. From the Department of Public Health.

BRODY, E. B.: Psychologic tension and serum iodine levels in psychiatric patients without evidence of thyroid disease. Psychosomat. M., 1949, *11,* 70. From the Department of Psychiatry and Mental Hygiene.

BROWNING, H. C.: Homologous and heterologous growth of transplants of various tissues during the course of development in the mouse. Cancer, N.Y., 1949, *2,* 646. From the Department of Pathology.

BURR, H. S.: The Connecticut State Medical Society. J. Connecticut M. Soc., 1949, *13,* 950.

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CLIFFTON, E. E. AND WOLSTENHOLME, J. T.: Hypervolemia and associated changes in mice bearing a transplanted granulosa cell tumor. Cancer Res., 1949, *9,* 331. From the Departments of Surgery and Anatomy.

DEMING, C. L.: The modern surgeries of the prostate. Surg. Gyn. Obst., 1949, *89,* 547. From the Department of Surgery, Section on Urology.

EVANS, T. S. AND SAUNDERS, A. I.: Histologically benign hemangioma with tumor of the heart. J. Connecticut M. Soc., 1949, *13,* 722. From the Department of Medicine.

FLETT, J., PRATT, E. L., AND DARROW, D. C.: Methods used in treatment of diarrhea with potassium and sodium salts. J. Pediat., S. Louis, 1949, *4,* 604. From the Department of Pediatrics.

FOORD, EDWARD: Rubella in pregnancy—a review of recent literature. J. Connecticut M. Soc., 1949, *13,* 739. From the Department of Obstetrics and Gynecology.

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GOLDWASSER, R. A.: A simple apparatus for the automatic inoculation of culture media. Yale J. Biol., 1949, *22,* 67. From the Department of Internal Medicine.

GOLDWASSER, R. A.: The source of phosphorus in bacteriophage. Yale J. Biol., 1949, *22,* 1. From the Department of Bacteriology. Part of a thesis for Ph.D.

GOODRICH, F. W., JR. AND THOMAS, H.: A commentary on natural childbirth. J. Pediat., S. Louis, 1949, *3,* 613. From the Department of Obstetrics and Gynecology.

GREENE, H. S. N. AND STRAUSS, J. S.: Multiple primary tumors in the rabbit. Cancer, N.Y., 1949, *2,* 673. From the Departments of Pathology and Surgery.

HAVENS, W. P., JR., LLOYD, H., MELNICK, J. L., AND COLBERT, J. W., JR.: Complement fixation with fecal antigens in viral hepatitis. J. Infect. Dis., 1949, *85,* 139. From the Department of Bacteriology, Yale University, and Jefferson Medical College.

HOWLETT, K. S., O'CONNOR, J. B., SADUSK, J. F., JR., SWIFT, W. E., JR., AND BEARDSLEY, F. A.: Sensitivity of tubercle bacilli to streptomycin. The influence of various factors upon the emergence of resistant strains. Am. Rev. Tuberc., 1949, *59,* 402. From the Department of Medicine in conjunction with the Laurel Heights State Tuberculosis Sanatorium.

KAADA, B. R., PRIBRAM, K. H., AND EPSTEIN, J. A.: Respiratory and vascular responses in monkeys from temporal pole, insula, orbital surface and cingulate gyrus. J. Neurophysiol., 1949, *12,* 347. From the Laboratory of Physiology.

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LIEBOW, A. A., WARREN, SHIELDS, AND DECOURSEY, ELBERT: Pathology of atomic bomb casualties. Am. J. Path., 1949, *25,* 853. From the Army Institute of Pathology, Atomic Energy Commission, Naval Medical Research Institute, and the Department of Pathology, Yale University School of Medicine.

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MICHAEL, S. T.: Adaptation to brief stress. Yale J. Biol., 1949, *22,* 71. From the Department of Psychiatry and Mental Hygiene.

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MYLON, E. AND FREEDMAN, L. R.: On the occurrence of renin in the blood of hypertensive patients. Am. Heart J., 1949, *38,* 509. From the Department of Pathology.

NEEDHAM, J. W.: The metabolism of potassium in diabetic acidosis. Yale J. Biol., 1949, *22,* 39. From the Department of Internal Medicine. Part of thesis for M.D.

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ROEMER, M. I.: Tuberculosis and its control in rural areas. Pub. Health Rep., Wash., 1949, *64,* 1269. Written while author was Director, Monongalia County (W.Va.) Health Dept.

ROTH, OSCAR AND DOFF, S. D.: Electrocardiograms of an unusual pattern in a patient with anomalous auriculoventricular excitation. Am. Heart J., 1949, *38,* 614. From the Department of Medicine, and the Medical Service of St. Raphael's Hospital, New Haven, Conn.

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SELDIN, D. W. AND TARAIL, ROBERT: Effect of hypertonic solution on metabolism and excretion of electrolytes. Am. J. Physiol., 1949, *159,* 160. From the Department of Internal Medicine.

SOLOMON, R. Z. AND SOLOMON, C. I.: Psychosomatic aspects of arthritis and allied disorders. J. Connecticut M. Soc., 1949, *13,* 1027. From the Hospital for Chronic Illness, Rocky Hill, Conn., and Department of Psychiatry and Mental Hygiene.

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BOOK REVIEWS

MALE AND FEMALE. By Margaret Mead. New York, William Morrow and Co., 1949. 477 pp. $5.00.

Margaret Mead has made an assumption, not necessarily held by all present day sexologists, that there is a fundamental difference between the human male and the human female, and has utilized four hundred and seventy-seven pages in impressive documentation of this thesis. Seven Southwest Pacific societies, from the stone age cultures of the New Guinean mountains to the ritualistic civilization of Bali and the modern United States, furnish the experimental material for an analysis of the effect of primary sex membership upon the development of the individual within the society and upon the society itself. Her approach is popular and we may well speculate upon the validity of some of her conclusions based upon limited observations in strange and inconvenient environments, but one is forced to admire the skill with which Dr. Mead has interwoven her data into a plausible and stimulating discussion of the cultural results of sex differences.

Her second chapter entitled, "How an Anthropologist Writes" stands as a brilliant apologia for the shortcomings of the anthropological method and a discriminating exposition of the field techniques by which this material was gathered. On the basis of this chapter, her insistance upon the basic differences in male and female assume a greater stature in terms of contemporary problems of sexual adjustment. If, as the author intimates, much of our present-day American marital misfunctioning springs from modern accentuation of the biological similarities of men and women and an over-emphasis of the competitive aspects of sex membership, the ultimate panacea may well be suggested by a comparative study of more primitive and stable societies. Time is short for such a comparison since the impact of western man has all but obliterated the stability of the remaining primitive cultures which suffer but a little time before they pass away.

V. M. CUTTER, JR.

THE NEUROSIS OF MAN. By Trigant Burrow. New York, Harcourt Brace & Company, 1949. xxvi + 428 pp. $7.50.

The Neurosis of Man is the sum of all the social evils which man creates for himself. The author attempts to construct a social psychology based upon what he calls phylopathology (defined in the glossary as "the term denoting the scientific investigation of the underlying factors in behaviour disorders envisaged from the background of phylobiology. It represents a broad organismic approach to deviations in behaviour, and includes oneself and the so-called normal community along with the neurotic patient." *Phylobiology* is defined as "the science of behaviour that studies the relation of the organism as a whole in its adaptation to the environment and to other organisms").

The book is divided into two parts. Part I deals with Interrelational Man or the Symptomatology of Human Behaviour, a Phyloanalysis; Part II with the Organismic Man or the Biology of Human Behaviour, a Phylosynthesis. There is an appendix in which instrumental recordings are presented, along with photographs of eye movements. A glossary and an index complete the format of the book.

In the author's Foreword, we learn that the history of phylobiology is the history of thirty years' association of the author and one Clarence Shields who is given no further introduction until page 204 when we find that he is President of the Lifwynn Foundation in Westport, Connecticut, where the investigations that produced this book were done. The thesis with which they began their work is stated as follows: "What man is overtly, is not what man is basically. Today human relations are throughout superficial, not fundamental. They are psychosocial not biological." The author says he lost interest in individual behaviour and Man became his centre of interest. He summarizes the purpose of his group experiment (Chapter 7) as follows: to divorce "from the concept or symbol the entire sum or system of effects which through their linkage with the symbol, have established in man a falsely systemized personality, a spurious centre of identity and hence an artificial basis of human motivation." This purpose and the method to achieve it were "more valiant than decisive" until the factor of tension was given consideration. This forms the bridge which takes the reader into the second half of the volume.

The second part of the author's thesis deals with the discovery that his problem was physiological in a social sense (p. 184) and with this discovery the "way had been opened to phyloneurology" (term "applied to neural modifications that affect the behaviour of man as a phylum"). In the species Man, "the brain has assumed a function that departs from the behaviour typical of the phylic brain of man." The author then discusses the form this departure has taken. In the next chapter he talks about contrasting patterns of tension which he calls the physiological seat of the Neurosis. The remainder of the book is devoted to a discussion of the "Biological Norm of Human Behaviour" and instrumental evidence for this and for deviations from it. Chapter XIII is a summary and Chapter XIV is called "Phylobiological Reflections" and is a sort of philosophical statement of faith in "the arduous work" of the author.

The above is a very brief sketch of the book's contents.

About the author one may say that Dr. Burrow is much concerned with the woes of the world. However, his claim to having formulated a science of human behaviour (even an elementary one) is a pretension cloaked in newly coined terms, and hidden behind abstractions so complex as to defy understanding. Here is an example: "This phylosomatic readjustment is coterminous with the abrogation of ditention. It is coterminous with the abrogation of the purely fanciful images that have replaced the reality of man's organismic security and have led to his bionomic undoing. The realignment of the function of the third or semiotic nervous system with the function of the cerebrospinal and autonomic systems will mean for man

the restoration of his organism's uniformity of motivation as a whole. Furthermore, with his concomitantly greater bionomic facility in communication through the spoken word or symbol, this functional realignment will contribute immeasurably to the adjustment of human relations throughout social groups" (p. 293).

It is understandable why to a man of Dr. Burrow's astronomical fancy the relatively simple, clear, and sound basic behavioural science of psychoanalysis is so unappealing. He wishes to cure the world (Author's Foreword, xiv) and do it quickly, no doubt; to which purpose the slow and painful method of the Freudian psychology is much too plodding. Dr. Burrow has rigged up some 'hi-falutin' telescopes at Lifwynn and trained them on the human race. What he discovered, however, were not people but *words.*

HENRY WEXLER

RAPID MICRO-CHEMICAL METHODS FOR BLOOD AND CSF EXAMINATIONS. By Fritz Rappaport. New York, Grune & Stratton, Inc., 1949. xvii + 404 pp. $8.75.

This book contains detailed descriptions of over a hundred clinical biochemical laboratory procedures ranging from rough qualitative tests to procedures usually employed only in clinical research. Many of the methods have been devised or modified by the author, and all have been tested in his former laboratory in Vienna or present laboratory in Petach Tiqua, Israel. Some of the methods have been adapted for use in tropical climates; others have been modified to circumvent wartime shortages. In his preface the author states that he had avoided the use of expensive equipment such as photometers and photoelectric colorimeters, an approach which will be of less value to those who have accepted such instruments as indispensable aids. Each method is clearly outlined with excellent diagrams of apparatus, and the underlying principles are explained. The criticism can be made, however, that when alternative methods are described for a given determination, no indication is given of their relative accuracy or reliability. Clinical interpretations are provided for each determination. These are, however, at times inaccurate and misleading. One gains the impression from this book that one might have from going over the laboratory notebook of one who has done much painstaking work in the field. Much useful information is provided, but it is not a book that will necessarily direct a reader to the available method best adapted to his needs.

ETHAN A. H. SIMS

CHYMIA. ANNUAL STUDIES IN THE HISTORY OF CHEMISTRY. Tenney L. Davis, Editor-in-Chief. Philadelphia, University of Pennsylvania Press, Volumes I and II, 1948 and 1949. xiv + 190 and x + 143 pp. $3.50 and $4.00.

In inaugurating this new series, a distinguished group of historians of chemistry, headed by the late Dr. Davis, have made a notable service to international scholarship in the history of science. Some inkling of its scope,

and of the importance of its contributions, may be gained from the contents of the two volumes that have appeared thus far.

Volume I

Recently acquired information concerning Frederick Accum, 1769-1838	C. A. Browne
A memorial tribute to Dr. C. A. Browne, with a bibliography of his contribution to the history of chemistry	C. K. Deischer
The argument of Morein and Merlin—An English alchemical poem	F. S. Taylor
Thomas Thomson—Pioneer historian of chemistry	H. S. Klickstein
L'École des chimistes français vers 1840	M. Daumas
Factors which led Mendeleev to the periodic law	H. M. Leicester
The early use of potassium chlorate in pyrotechny—Dr. Moritz Meyer's colored flame compositions	T. L. Davis
The early chemical and pharmaceutical history of calomel	G. Urdang
The concepts of substance and chemical element	J. R. Partington
Priestley settles the water controversy	S. M. Edelstein
Scottish alchemy in the seventeenth century	J. Read
Carl Wetzein and the congress at Karlsruhe	C. de Milt
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The beginnings of laboratory instruction in chemistry in the U.S.A.	H. S. van Klooster
An Irish-American chemist, William James MacNeven, 1763-1841	D. Reilly
Was Newton an alchemist?	R. J. Forbes
Brenngläser als Hilfsmittel chemischen Forschens	R. Winderlich
Désormes et Clément découvrent et expliquent la catalyse	P. Lemay
History of ambergris in India between about A.D. 700 and 1900	P. K. Gode
Some personal qualities of Wilhelm Ostwald recalled by a former assistant	E. P. Hillpern
The experimental origin of chemical atomic and molecular theory before Boyle	R. Hooykaas
Das chemische Laboratorium der Bayerischen Akademie der Wissenschaften in München	W. Prandtl
Pulvis fulminans	T. L. Davis
Some seventeenth century chemists and alchemists of Lorraine	D. I. Duveen and A. Willemart
Sir Kenelm Digby, alchemist, scholar, courtier, and man of adventure	W. Miles

J. S. FRUTON